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THE AMERICAN PHYSIOLOGICAL SOCIETY

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VOL. 22, NO. 1

Issued January, 1942

BALTIMORE, U. S. A.

Entered as second-class matter, January 15, 1921, at the Post Office at Baltimore, Md., under the act of March 3, 1879

Made in United States of America

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PHYSIOLOGICAL REVIEWS

VOL. 22 JANUARY, 1942 No. 1

THE INSENSIBLE LOSS OF WATER

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Water is being continuously evaporated from the lungs and skin. At times there is an additional loss from the skin in the form of liquid water. This insensible loss of water because of its magnitude, is an important fraction of the water excreted by the organism. Further, since it requires 0.58 calory to evaporate one gram of water, the vaporization of water is one of the means for removal of heat. This loss of water, both gaseous and liquid, is designated "the insensible loss of water." This phenomenon is the main cause of the insensible loss of weight.

It is more than 300 years since Sanctorius, suspended from one arm of a beam balance, observed that he lost weight progressively even though he eliminated neither urine nor feces. But the true nature of this "perspiratio insensiblis," as it was named by its discoverer, was not understood until comparatively recent times.

THE RELATIONSHIP OF INSENSIBLE LOSS OF WATER TO INSENSIBLE LOSS OF WEIGHT. Isenschmidt (1) expressed this relationship in the form of an equation:

$$I.L.^{1} = I.W. + CO_2 - O_2.$$

It is evident from a consideration of Isenschmidt's equation that *I.W.* can be calculated from *I.L.* when the weights of CO_2 and O_2 are known. When the metabolic mixture is such that the weight of the carbon dioxide excreted equals the weight of the oxygen absorbed, $I.W. = I.L.$ This condition exists when the respiratory quotient is 0.725. As the proportion of carbohydrate in the metabolic mixture increases, the weight of the carbon dioxide becomes progressively greater than the

[1] *I.L.* equals insensible loss of weight in grams. *I.W.* equals weight of water vaporized in grams. CO_2 equals weight of carbon dioxide produced in grams. O_2 equals weight of oxygen absorbed in grams.

weight of the oxygen and *I.W.* is a correspondingly smaller fraction of *I.L.* On the other hand, if fat alone were being metabolized *I.W.* would be slightly greater than *I.L.* Mitchell and Hamilton (2) have shown that this ratio $\frac{I.W.}{I.L.}$ is also modified by the per cent of the total heat, removed by vaporization of water. To see clearly the effect of different respiratory quotients on this ratio one must deal with a fixed per cent of heat lost by vaporization of water. For example, when 25 per cent of the heat is lost by evaporation of water at an R. Q. of 0.707, $\frac{I.W.}{I.L.}$ = 101.6 per cent; while at an R. Q. of 1.00, it is only 79.9 per cent. At the usual basal R. Q. of 0.825, $\frac{I.W.}{I.L.}$ is 91.2 per cent.

The effect of shifts in the amount of heat lost by vaporization may be seen from the following considerations. An individual in 24 hours absorbed 537 grams O_2 and excreted 573 grams of CO_2 and produced 1772 calories. The R. Q. was 0.777. His insensible loss of weight for the period was 757 grams. From Isenschmidt's equation, the *I.W.* was 721 grams. He lost 23.6 per cent of the heat by vaporization of water $\left(\frac{721 \times 0.58}{1772}\right)$ and $\frac{I.W.}{I.L.} = \frac{721}{757} = 95.2$ per cent.

Assuming that the heat production and the metabolic mixture remain the same but the amount of heat lost by vaporization of water is now 47.2 per cent, *I.W.* would be 1442 grams and therefore *I.L.* would be 1478 grams and $\frac{I.W.}{I.L.}$ would be 97.6 per cent. Clearly the effect of change in per cent of heat removed by vaporization is much smaller than that caused by shifts in R. Q. As Mitchell and Hamilton have pointed out, at any given R. Q. as the per cent of heat removed by vaporization increases, *I.W.* approaches *I.L.* These relationships are summarized in their table 1 which is reproduced here.

Partition of I. W. By definition *I.W.* includes all of the water vaporized plus any water which leaves the skin in the liquid state. This bifold loss of water takes place when the heat production is very great and the environmental conditions do not favor evaporation. It may also occur in quiet states when the relative humidity approaches 100 per cent and the air temperature is high. Even under extreme conditions, this loss of liquid water is never more than a small part of *I.W.* Accordingly under ordinary circumstances one has to deal only with vaporized water. Water is vaporized from both the respiratory tract and the skin.

Respiratory tract. The amount of water vapor leaving the respiratory tract is related to the temperature and water content of the inspired air and to the volume of air breathed. Benedict and Benedict (3), with their usual precision, determined separately the loss of water from the respiratory tract and skin. When the subjects breathed dry oxygen at room temperature the basal values for loss from the lungs varied from 8.8 grams to 12.05 grams per hour for one woman and two men. This was close to 40 per cent of *I.W.*

The relationship between lung ventilation and weight of water vapor lost from the lungs is seen when subject B increased his ventilation from 369 liters to 891 liters per hour. The corresponding lung waters were 12.5 grams and 23.58 grams.

TABLE 1 (2)

The percentage of the insensible weight loss represented by vaporized water for various values of the respiratory quotient

PERCENTAGE OF HEAT LOST AS VAPORIZED WATER	PERCENTAGE LOSS AT RESPIRATORY QUOTIENT OF						
	0.707	0.75	0.80	0.85	0.90	0.95	1.00
20	102.0	96.8	91.6	87.0	82.9	79.3	76.1
25	101.6	97.4	93.1	89.3	85.8	82.7	79.9
30	101.3	97.9	94.2	90.9	87.9	85.2	82.7
35	101.1	98.2	95.0	92.1	89.5	87.0	84.8
40	101.0	98.4	95.6	93.0	90.7	88.4	86.4
45	100.9	98.6	96.1	93.8	91.6	89.6	87.7
50	100.8	98.7	96.4	94.3	92.4	90.5	88.8

In 1930, Jores (4) obtained essentially similar results, using the same technic, for the partition of water vapor between lung and skin.

Since in both cases the subjects inspired dry oxygen it is instructive to examine the values obtained when room air is breathed. Galeotti (5) found that at a room temperature of 12.5°C. the water content of the expired air was 0.0326 gram per liter when the water content of the inspired air was 0.0034 gram per liter (relative humidity 30 per cent). The difference is approximately the amount of water contributed to the expired air by the respiratory tract, namely, 0.0292 gram per liter. When the temperature was the same but the water content of the inspired air was 0.0075 gram per liter (relative humidity 68 per cent), the expired air contained 0.0322 and the difference was 0.0247 gram per liter. The effect of relative humidity is evident. The temperature effect is seen from average values when the air temperature was 24°C.

and the water content of inspired air was 0.0115 gram per liter (relative humidity 50 per cent), the average water content of expired air was 0.0366. The difference is 0.0251. Unfortunately the author did not study the effect of the lower temperature at this relative humidity. However, if one averages the values obtained at 12.5°C. for the two humidities used (30 and 68 per cent) one obtains a value of 0.0270 gram per liter. If this number is compared with 0.0251, it is seen that increasing the temperature of the inspired air with relative humidity unchanged, causes a lessened loss of water from the respiratory tract.

Further information about the effect of the moisture of the inspired air is reported by Adachi and Ito (6). Their data are especially interesting because they show that the vaporization from the skin increases to compensate for a diminished loss from the lungs. When the subject breathed dry air, the loss per hour from the lungs was 7.90 grams and from the skin 21.56. In contrast, the subject responded to inspired air saturated with moisture by losing only 4.30 grams per hour from the lungs, but the evaporation from the skin increased to 23.6 grams.

While water content of the inspired air has more effect upon the loss of water from the respiratory tract than temperature, both effects are small when the subject is quiet.

There has been confusion in the literature concerning the question whether the expired air is saturated with water vapor. This apparently arose because it was assumed that the temperature of expired air is 37°C. Galeotti (7) measured the temperature of expired air by means of a thermocouple at room temperature from 16 to 35°C. and found it to vary between 34.4 and 35.7°C. At these temperatures it was 90 per cent saturated. The water content was only 78 per cent of that of saturated air at 37°C.

This loss from the respiratory tract is then controlled by the physical conditions of the environment, and by only one biological factor—the lung ventilation. The volume of air breathed, barring voluntary effects, is related directly to heat production.

Skin. The evaporation from the skin is affected by the following factors: environment, humidity, temperature and air currents, circulation of blood through skin, character of skin covering, water content of body.

Investigators have recorded these effects upon either *I.L.* or *I.W.*, not upon the loss from the skin separately.

Humidity. For the nude male subject in the basal state when the environmental temperature was fixed at 28°C., Wiley and Newburgh

(8) obtained the following values for *I.W.* per hour: 22, 17, 15, 14 grams for relative humidities of 20, 40, 60 and 80 per cent respectively. On the other hand, the subject, comfortably clothed, vaporized the same amount of water when the relative humidity varied from 20 to 60 per cent. This was confirmed by Van Harreveld, Grutterink and Noyons (9) who found little effect on *I.L.* for variations of plus or minus 35 per cent relative humidity; and by Ginandes and Topper (10) who recorded not more than 10 per cent variation in I.L. of children when the relative humidity varied from 19 to 74 per cent. However, the *I.L.* was lessened by humidities above 74 per cent and increased when it was less than 19 per cent. Clearly, then, the *I.W.* of the comfortably clothed subject is affected only by extreme dryness or wetness of the air.

Temperature. Figure 1 (8) shows the interrelationship between heat production, skin temperature and total *I.W.* at room temperatures from 18°C. to 40°C. at a relative humidity of 20 per cent. The male subject was nude, fasting and recumbent. It will be seen that even though the heat production was greatest at 18°C., at this temperature the *I.W.* was at its lowest value. At this point the skin temperature was at its lowest level also. As the skin temperature decreased from 34°C. to 29°C., the *I.W.* also decreased slowly and uniformly. The total decrease was about 115 grams.

This ability of the organism to decrease vaporization of water through the skin is even greater than it appears since with the same relative humidity the amount of water evaporated from the lungs must have increased as the environmental temperature fell.

Further inspection of figure 1 shows that the *I.W.* began to increase rapidly at about 30°C. This abrupt change implies that a second factor has now been added to the mechanism, which permitted an increase in the vaporization of water that amounted to 465 grams per 24 hours per degree change in environmental temperature at the higher temperatures, as contrasted with 11 grams at the lower. This huge increase is attributable to the activity of the sweat glands.

The relative contribution to the maintenance of the homeothermic state by the integument, aided and unaided by the sweat glands, may be realized from studies on individuals without sweat glands.

In 1911 Loewy and Wechselman (11) showed for the first time that the human being can lose water through the skin in the absence of sweat glands. Examination of 600 sections of axillary skin did not reveal a single sweat gland. They studied the response of the skin of the leg by enclosing it in a metal cylinder so arranged that the water vaporized from the skin

could be measured. They found that the patient lost about the same amount of water vapor per square meter and hour as the control in the basal state, and they concluded that simple physical diffusion of water vapor through the normal skin occurs and that this is the total loss from the skin when no special demands for removal of heat exist. The sweat

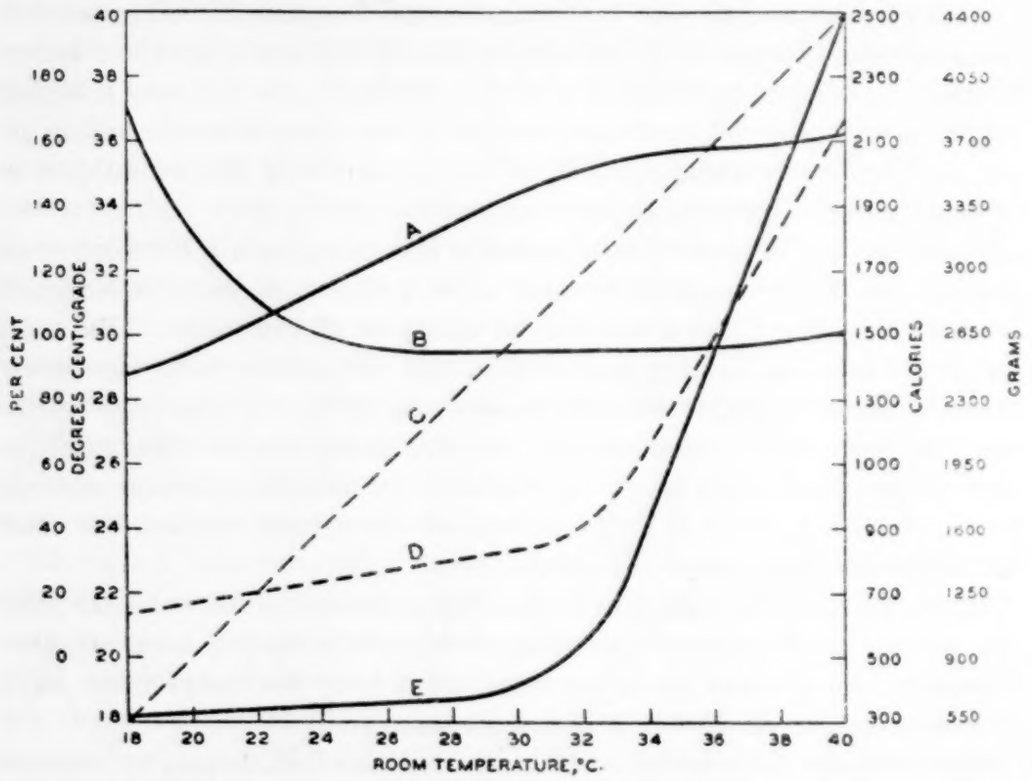

Fig. 1. Nude subject. The effect of room temperature on skin temperature, basal heat production and the dissipation of heat by the vaporization of water at a relative humidity of 20 per cent.

A. Skin temperature in degrees centigrade. *B*. Basal heat production in calories per 24 hours. *C*. Rate of increase in room temperature. *D*. Heat lost by the vaporization of water in per cent of the total heat dissipated, or grams of water vapor per 24 hours. *E*. Heat dissipated by the vaporization of water in calories per 24 hours.

glands are only intermittently active, i.e., during great muscular activity and in hot environments.

Richardson (12) studied a 14 year old boy, examination of whose skin revealed no sweat glands. At rest in the calorimeter when the temperature was 24 to 25°C. the amount of water vaporized compared favorably with the control. The extra heat produced by exercise at this same

p. 6: The column at the right of figure 1, designated "grams," should start at 517 and increase by 345 for each interval. In the legend of this figure the phrase "or grams of water vapor per 24 hours" should be transferred to the end of the last sentence.

calorimeter temperature was eliminated by the patient nearly as well as by the control but the per cent removed by vaporization was somewhat less on the part of the patient. But when the patient, except for his head, was enclosed in a bag and the temperature of the air passing through it was 48 to 49°C., he lost 33 grams per hour insensibly. The control under the same conditions lost 336 grams. By separating the loss from the skin and lungs it was shown that the patient evaporated 22 grams per hour from the skin at rest when exposed to an environmental temperature of 24.5°C. At the same time, 9 grams were lost from the respiratory tract.

The most recent study of this condition was made by Sunderman (13). His two patients and two controls were exposed to environmental temperatures of 43.3°C. for 30 minutes. The oral temperatures of the controls remained normal and the *I.Ls.* were 262 and 360 grams. But the oral temperatures of the patients rose to 101.4 and 102.0°F., and they lost only 22 and 15 grams insensibly. The basal insensible losses of these two patients were normal.

Air currents. Benedict and Benedict (3) recorded the loss of water vapor from the skin on the part of a nude female subject in the resting state at an environmental temperature of 21°C., before and while exposed to air movements produced by a blower. The values were 11 grams and 10.2 grams per hour.

DuBois (14) in carefully conducted experiments recorded the separate fractions of heat loss by means of the calorimeter. The nude male subject was in the post-absorptive state, lying quietly and exposed to an environmental temperature of 29°C. Without the fan he lost 30 grams *I.W.* per hour which accounted for a loss of 30 per cent of the heat. With the fan, the *I.W.* was 37 grams—a loss of 26 per cent of the heat because the total loss of heat had increased. This is especially instructive since in quiet air only 11 per cent of the heat was removed by convection, whereas the fan increased this loss to 33 per cent.

Sex differences have been observed by Hardy (15) and co-workers. Nude female subjects, when exposed to the same conditions as nude men in the calorimeter, showed a slightly lower *I.W.* per square meter per hour at temperatures from 22 to 29°C. At the latter temperature sweating began in the women, but was delayed until 31°C. for the men. The larger question of heat regulation as related to sex is carefully studied by these authors.

Clothing. Having now dealt with the responses of the nude subject to environmental temperatures, the protective effect of clothing will be

shown. It is obvious that clothing will not prevent the onset of sweating at the point at which it would occur in the nude subject. However, Wiley and Newburgh (8) showed that protection by means of heavy pajamas caused their subject to have a constant *I.W.* for environmental temperatures from 24 to 30°C. Below 24°C. he behaved as did the nude subject in regard to *I.W.* Had he been further protected against cold it seems evident that the range over which *I.W.* would have been constant would have reached much lower temperatures.

Circulation through skin. The organism may be thought of in terms of a moist protoplasmic mass enclosed in an integument that permits only a limited amount of water to diffuse outward. The actual amount of diffusion is related to the volume of the circulation through the skin and to its temperature; but the organism is capable of increasing *I.W.* far beyond this limited amount through the activity of the sweat glands.

Wiley and Newburgh's (8) subject was able to vaporize about 18 grams per square meter an hour before sweating took place. But the organism frequently loses by diffusion less than the greatest possible amount of water. For example, this same subject, whose heat production had been increased about 33 per cent above the basal level, vaporized 17.7 grams per square meter per hour when the skin temperature was 32°C. At the same skin temperature in the basal state he vaporized only 16 grams. This restriction is brought about by changes in the volume flow through the skin. One effect of lessening the flow is fall in temperature of the surface of the body. When this took place in Wiley and Newburgh's (8) subject the decrease in water vapor at the lower skin temperature followed closely the predicted values corresponding to the change in vapor pressure. Barbour (16) reached the same conclusion, working with cats. He also showed that the hemoconcentration which occurs as part of the response to cold did not affect vapor pressure significantly. But since different actual amounts of water may be vaporized per unit of surface at the same skin temperature, the latter cannot be the only controlling factor. It is believed that the integument, flooded with blood, can lose water vapor more easily than when it is caused to become relatively dry by curtailment of the circulation. The volume flow, in its turn, is controlled by the vasomotor apparatus. Hardy and Oppel (17) have shown how extremely sensitive the skin is to changes in environmental temperature; and these responses are signals to the vasomotor center.

Return to the sweating apparatus affords the opportunity of appreciating to what extent the integument resists the loss of body water. The subject studied by Wiley and Newburgh (8) when exposed to a room

temperature of 40°C., vaporized 107 grams of water per square meter and hour. The skin temperature was 36°C.; however, when he was exposed to an environmental temperature of 29°C., he vaporized only 18 grams. The skin temperature was now 34°C. These differences in skin temperatures account for only a very small part of the change. The sweat glands, in the first case, pumped water onto the skin and the environment quickly carried it away. As organisms gradually passed from the waters to the dry land, it was necessary to develop means of conserving water. This was accomplished in part by decreasing the permeability of the skin. However, with the development of the homeothermic state, a mechanism working in the opposite direction came into existence to protect the organism from overheating when the metabolism was accelerated.

The dog, almost devoid of sweat glands, pants to rid himself of heat when man would sweat. Polypnea is effective for two reasons. First the rapid fanning of the wet tongue is an efficient method of vaporizing water, but the area is so small that it may not be sufficient. A second gain is made by virtue of the shallowness of the respiration. Christie and Loomis (18) have shown that rapid shallow breathing is a successful method for the elimination of heat without causing a serious loss of CO_2.

Water content of body. Manchester, Husted and McQuarrie (19), in 1931, believed that they had shown that diminution in water content of body reduced *I.W.*, but Newburgh and Johnston (20) were not convinced that the data were gathered with sufficient care to establish the point. They found that reduction of the body water by approximately 6 per cent did not reduce *I.W.* Their subject, who weighed 60 kilos, was caused to lose 2863 grams by withholding water and feeding 10 grams of NaCl daily. This represents a loss of approximately 6 per cent of his body water. Dehydration of this magnitude did not significantly affect *I.W.* Levine and Wyatt (21) determined the basal *I.L.* of the same infants before and after dehydration. The latter state was accompanied by reduction of 11 per cent in *I.L.* but, as they point out, the large fall in R. Q. that is observed in dehydrated infants may account for 8 per cent in the shift in *I.L.*

Hall and McClure (22) confirmed Newburgh and Johnston in their conclusion that *I.W.* is not affected by dehydration of 6 per cent or less, but showed that greater dehydration did lower *I.L.* Even though there has been a great deal of controversy about this question in the past, the experiments of Hall and McClure were conducted with such care that their conclusions may be considered final.

They next took up the question of an effect on *I.L.* of flooding the

body with water. They found that ingestion of as much as 3700 cc. of water in 3 hours did not change the rate of *I.L.* Ginandes and Topper (10) likewise observed no effect in children from ingestion of large amounts of water. However, when they (23) gave 5 to 15 grams of NaCl in capsules to 9 children, 6 to 10 years of age, they invariably observed a marked reduction in *I.L.* from 15 to 30 per cent. The heat production remained unchanged. This reduction began about one and one-half hours after administration of the salt and lasted about two hours. Gilman and Barbour (24) earlier demonstrated a similar response in rabbits and recorded simultaneous wide shifts in osmotic pressure of the blood. However, Barbour (16) pointed out in a later publication that such increases in osmotic pressure could not account quantitatively for the effect on *I.L.*

It should be noted that Gilman and Barbour (24) gave 1.7 grams of NaCl per kilo, and that Ginandes and Topper (23) gave from 0.3 to 0.7 gram per kilo. However, when Hall and McClure (22) gave about 0.2 gram NaCl (1200 cc. 1 per cent sol.) to adult human subjects, they were unable to observe any effect on *I.L.*

How does the extra accumulation of fluid in the body which occurs in edematous patients affect *I.W.*?

Beginning with a publication in 1929, Zak (25) has maintained that patients suffering from congestive heart failure are able to absorb water from the air. In response to adverse criticism, he later stated (26) that this phenomenon could not be demonstrated in all edematous cardiacs and that weighings had to be made every half hour because an insensible gain in weight might take place only once in many hours. In 1939, his pupil, Neurath, (27) published observations which appeared to him to further substantiate the possibility of this "negative insensible perspiration." We have difficulty in accepting his evidence based on two cases. The second one was an obese but otherwise normal individual who, following a morning weighing, received a large dose of mercurial diuretic intravenoulsy. During the next ten hours, according to the record, no urine was voided. He lost 2790 grams insensibly. During the next 13 hours, the urine amounted to 1568 grams and he gained 788 grams insensibly. We are puzzled by the anuria since the previous subject produced 1059 grams of urine and again 1087 grams in the 5 hours immediately following the diuretic.

On the other hand, Heller (28), Jores (29), Gereb and Laszo (30), Magendantz and Stratmann (31), Gabriel and Kahler (32) and later, Kahler and Schmidt (33), and Kesterman and Schleining (34) never

recorded an insensible gain in weight in the many edematous patients studied by them.

A study made in this laboratory by R. H. Freyberg (35) of a far advanced nephritic disclosed entirely normal *I.L.* throughout. The pertinent data are brought together in table 2. The patient had been freed of edema a few days earlier. The diet was identical throughout. The daily fluid intake varied only between 3800 and 4000 grams. It will be seen that the small variations in *I.W.* are of the same order of magnitude when he was edema-free or whether he was gaining or losing

TABLE 2

DATE	BODY WEIGHT	I.L.	I.W.*	
	kilos	*grams*	*grams*	
Nov. 12	53.916	1,209	1,138	
13	53.850	1,103	1,031	
14	53.818	1,182	1,116	
15	53.998	1,227	1,157	10 gms. NaCl
16	54.953	1,184	1,113	10 gms. NaCl
17	56.009	1,060	987	10 gms. NaCl
18	57.073	1,200	1,114	
23	55.555	1,114	1,041	8 gms. NH_4Cl
24	52.220	1,172	1,101	8 gms. NH_4Cl
25	54.722	1,111	1,039	8 gms. NH_4Cl
26	54.487	1,219	1,148	8 gms. NH_4Cl
27	53.584	1,231	1,161	8 gms. NH_4Cl

* $(CO_2 - O_2)$ calculated from metabolic mixture.

edema. We know of no unequivocal evidence that *I.W.* is affected by gain or loss of edema fluid.

Is there any reasonable explanation for the alleged insensible gain in weight? Two suggestions have been made. The first one is concerned with absorption of water by the skin itself. A search through the literature has disclosed no satisfactory experiments which show how much water can be taken up from a water bath or moist air. The former has been studied by Moog (36) and Eimer (37) but the data are not satisfactory. It is clear, however, that the organism after being depleted of water continues to lose weight insensibly when immersed in water. Moreover, Wiley and Newburgh's (8) nude subject, exposed to an atmosphere whose relative humidity was 20 per cent and whose

temperature was 28°C., had an *I.W.* of 21.6 grams per hour. At 80 per cent himidity, at the same temperature, he lost 14.4 grams per hour. They attributed this decrease to the increased vapor pressure of the atmosphere. From the meagre evidence at hand it seems highly improbable that the human skin can absorb significant amounts of water from moist air. We find no satisfactory evidence to support the view that any water can be secreted inward.

The second suggestion assumes that oxygen is retained in the production of glucose from non-carbohydrate precursors (Silva-Mello, 38). Obviously the new glucose would have to be retained. Heller (39) calculates that this cannot account for an insensible gain in weight.

There are many pitfalls in the measurement of *I.L.* Mattresses, bedding and clothing absorb and lose water rapidly when exposed to changing humidities. The common use of wooden bed frames is objectionable since they also absorb and lose water. The thirst caused by restricted intake of fluid tempts patients to obtain water surreptitiously. All of these things should be borne in mind when evaluating the data in this field. It does not as yet seem necessary to accept the proposition that either the normal or abnormal individual ever fails to exhibit an insensible loss of weight.

Relation to heat elimination. The use of the respiration calorimeter necessitated the collection of the water vaporized as a means of measuring the heat removed by this process. As early as 1907, Benedict (40) reported that an average value of 22 per cent of the total heat eliminated, was removed by vaporization of water with a variation from 19 to 30 per cent. The per cent was essentially the same for the basal state and after food. Later Soderstrom and Du Bois (41) published a large number of observations which ranged from 21 to 32 per cent with an average of 25 per cent. Levine and Wilson (42, 43) obtained similar values for infants and children.

These observations make it clear that the comfortable quiet individual rids himself of an approximately fixed percentage of the heat of his metabolism by vaporization of water.

Since in the basal state *I.W.* is almost a constant portion of *I.L.*, it is evident that the latter may be employed as an indirect measure of total heat loss. Benedict and Root (44) presented an excellent review of the earlier literature and they formulated a table for predicting basal heat production from basal *I.L.* obtained by consecutive 10 to 15 minute periods. In 1930, Levine and Marples (45) published a satisfying treatment of this general question. They analyzed statistically 196

cases in which there were available simultaneous measurements of heat production and basal *I.L.* The data for adults were obtained in the Russell-Sage calorimeter (41) and those for infants and children in the respiration chamber at the New York Nursery and Child's Hospital (46, 47).

The high coefficient of correlation, 0.9417 ± 0.0064, shows the close relationship between the *I.L.* and heat production. The smoothed curve derived from plotting these two variables against each other takes the form of a straight line which may be used for predicting heat from *I.L.* Several other investigators (4, 48, 49, 50) have studied this same relationship. A study of Levine and Marples' data reveals that essentially the same per cent of heat is removed by vaporization of water at all levels of heat production. These values as calculated by Heller (49) are 27.6 per cent at 500 calories and 24.2 per cent at 2,000 calories. Ginandes and Topper (50) in 56 observations on 27 children from 4 to 15 years of age, obtained a line whose slope resembled that of Levine and Marples but at the lower end, 32.6 per cent of the heat is removed by vaporization, whereas at the upper end the per cent is 25.7. Heller and Schwartz's (51) curve is identical with that of Levine and Marples at the upper end of the line in respect to per cent of heat vaporized but the slope of their line is a little steeper. It should be noted that their material included increases in heat production produced by food and exercise.

On the other hand, if one plots in the same way the data of the following investigators separately, Benedict and Root (44), Jores (4), Heller (49) and Laszlo and Schurmeyer (48), one obtains a series of divergent lines which depart widely from Levine and Marples. This means that the per cent of total heat lost by vaporization of water must have varied widely. Thus, at heat productions of 900 calories in Benedict and Root's series, the per cent is 19.4, whereas at 2,000 calories it is 31.3. If the line is continued downward, the *I.L.* would disappear just below 500 calories as pointed out by Heller (49). It should be noted that this latter group of investigators used for the most part abnormal subjects.

Newburgh and his associates (52) compared the 24-hourly *I.W.* with heat production of normal subjects determined by indirect calorimetry. In 29 experiments on 9 subjects they obtained an average value for the percent of heat lost by vaporization of water of 25.1 with a range from 21.2 to 27.7 per cent. When the *I.L.* of these subjects is plotted against the heat productions, the slope of the line thus obtained corresponds

almost exactly with that of Levine and Marples. Therefore, it seems to be true that not only does the human organism tend strongly to rid itself of close to 25 per cent of its heat by vaporization of water in the quiet, comfortable state from infancy through old age, but that the normal adult follows the same principle throughout the 24 hours. Levine and Wheatley (53), in a careful study, were unable to demonstrate this relationship for the 24 hours in infants. Since this relationship presumes that the subject is comfortable as regards the environment it is evident that one cannot know whether this condition exists in the case of infants.

Since it is in general true that 25 per cent of the total heat is lost by vaporization of water and since it is also true that heat production may be predicted from *I.L.* (obtained under carefully controlled conditions), it follows that the usual shifts in R. Q. do not change the relationship between *I.W.* and *I.L.* significantly. At present, the best data for prediction of heat from *I.L.* is represented by Levine and Marples' (45) smoothed curve.

I.W. in lower species. It has been learned from the study of man that the percent of heat lost by vaporization of water is closely related to the environmental temperature and that in the "comfort zone" approximately 25 per cent of the heat is so lost. Since it is manifestly impossible to know when an animal is comfortable, the investigator is at a serious disadvantage. The literature records the percent of heat lost by vaporization for various temperatures but does not permit one to conclude what the percent is at the ideal temperature, for most species. However, it is well known that there is a narrow range of environmental temperatures over which the basal heat production has a constant minimal value (thermic neutrality). It may well be true that measurements of *I.W.* well within this range would reveal the same constancy of percent of heat lost by vaporization of water as occurs in man. It was shown early by Rubner (6[illegible]) that the dog responded like unclothed man to environmental temperature. When exposed to 25°C. his dogs lost 24.4 per cent of the heat by vaporization of water, whereas at an environmental temperature of 15°C., the percent was 13.8. It should be noted that both Greene and Luce (57) and Lee (60) did study their animals close to thermic neutrality and their data are therefore of special value.

In many of the species the number of observations is too few and experimental conditions were insufficiently controlled.

Table 3 brings together the data in the literature.

RELATION TO WATER EXCHANGE. In order to compare quantitatively the water available to the organism with the elimination of water, one must, in addition to measuring that which is ingested, calculate the amount produced by oxidation and also the preformed water released by catabolic processes or fixed by anabolic ones. On the outgoing side the value of *I.W.* must be determined, in addition to measuring the water content of the urine and stool. The water of oxidation is derived, by means of factors, from the metabolic mixture. The composition of the latter may be calculated from total heat production derived from *I.L.* and the urinary N by methods discussed by Newburgh and his

TABLE 3

SPECIES	INVESTIGATOR	ENVIRONMENTAL TEMPERATURE	PER CENT OF HEAT LOST BY VAPORIZATION OF WATER	
			Range	Average
		°C.		
Rat, fasting	Greene & Luce (57)	25–31	20.6–26.8	23.8
Rat, 24 hours	Greene (58)	23–27	20.8–21.6	21.3
Mouse	Benedict & Lee (59)	28		18
Rabbit	Lee (60)	28–29	17.7–29.7	24.6
Goose	Benedict & Lee (61)	16–29	15–40	
		18–22		16
Cow	Ritzman & Benedict (62)	16.9–23.2	17–34	26.1
		8.5– 9.8	14–15	
Cow	Kriss (63)	Uniform	22.3–37.3	27.6
Steer, sheared	Mitchell (2)	24.5	26.7–34	30.8
Elephant	Benedict (64)	20–24.7	17.2–19.1	18.3
Dog	Rubner (65)	25		24.4

associates (52). The preformed water is then calculated by comparing the diet with the metabolic mixture.

The nature of *I.W.* has already been discussed. It has been pointed out that it may be determined directly in the calorimeter or that it may be derived from *I.L.* From the strictly quantitative aspect the most satisfactory method is the determination of CO_2 output and O_2 absorption by means of the respiration chamber. Then *I.W.* may be derived from *I.L.* by employing Isenschmidt's equation. Since such facilities are limited and restricted in length of period and in activity of the subject, they cannot be widely used. Accordingly, Lavietes (54) and Newburgh and associates (52, 55, 56) discussed the manner in which

CO_2 and O_2 can be calculated from the metabolic mixture. Since these calculations assume carbohydrate balance and that the percent of the heat lost by vaporization of water is fixed at 25 per cent, errors of unknown magnitude may be present.

On the other hand, can it be assumed that *I.W.* is a fixed percent of *I.L.* under certain conditions? Consideration of Levine and Marples' (45) prediction where approximately 25 per cent of the heat was lost by vaporization of water, reveals that close to 94 per cent of *I.L.* is *I.W.* Furthermore, a study of data obtained in this laboratory (~~[illegible]~~) on a normal man fed a normal maintenance diet (P. 91, F. 186, CHO. 241 grams) for 18 days showed that $\frac{I.W.}{I.L.} \times 100 = 93$ per cent. When he was fed a supermaintenance diet (P. 89, F. 413, CHO. 445 grams) for 15 days the $\frac{I.W.}{I.L.} \times 100 = 88$ per cent. Since the first diet approximates the usual mixed one, the relation between *I.L.* and *I.W.* would be expected to be the same as the average one for the group reported by Levine and Marples. Accordingly, when ordinary maintenance diets are fed, it may properly be assumed that *I.W.* is 93 or 94 per cent of *I.L.* Supermaintenance high carbohydrate plans lower the percent toward 88. It is unlikely that it will ever be significantly lower. If, however, the carbohydrate metabolized is low because of dietary restriction, $\frac{I.W.}{I.L.}$ approaches one.

SUMMARY

The water vaporized from lungs and skin removes heat and also plays an important part in water exchange.

Its relationship to total insensible loss of weight and its partition between skin and lungs is discussed.

The effect of environmental temperature and humidity, air currents, clothing, blood flow through the skin, is dealt with.

The part played by the sweat glands is analyzed.

The relationship of water content of body to insensible water is discussed.

The use of the insensible water as a measurement of heat production is analyzed, as well as its place in the quantitative measure of water exchange.

The percent of heat removed by vaporization of water in lower species is noted.

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HEMOGLOBINURIA

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Hemoglobinuria, dramatically associated with a variety of pathological conditions, has doubtless always been a source of wonder and amazement to patients as well as a valuable diagnostic guide to clinicians. Experimentally it was first described about the middle of the nineteenth century and problems relating to the phenomenon have intrigued investigators ever since.

In all the earlier studies and in many that have appeared within relatively recent years, the emphasis is placed on the site rather than on the actual mechanism of renal hemoglobin elimination. The literature contains a group of conflicting theories, each of which tends to be documented in a self-perpetuating fashion and few attempts have been made to explain the phenomenon of hemoglobinuria in the light of facts uncovered in other fields of renal research. Due to the great variety of animals and methods used and to conclusions drawn from purely qualitative and often incomplete studies, comparison of many of the data in the literature is often difficult or impossible.

Experimental physiologists have presented and consistently substantiated the concept that, "beyond reasonable doubt, the central process in the formation of urine by the glomerular kidney is the separation at the glomerulus of a *protein free filtrate* of plasma, containing the diffusible constituents in *the same* concentration as in the plasma water, i.e., glomerular filtration" (42, Shannon, p. 63). This modern concept of renal function implies that the glomerular membrane, acting as a sieve, restricts the transfer of all molecules which are greater in diameter than the pores in the membrane. The filtration theory is supported by all the findings on the excretion of substances having a molecular weight of 15,000 or less (apparent molecular weight of inulin (8)) but does not attempt to explain the excretion of a large molecule like hemoglobin, except as a result of pathological glomerular changes. No recent attempt has been made to present an explanation of the fact that large molecules *are* excreted by the kidney, in apparently normal mammals,

which is adequately fitted into the theory which maintains as one of its major premises that these molecules *cannot* escape by way of the glomerulus.

Since in cases of experimental and clinical hemoglobinuria there is no reason to suspect any pre-existing kidney pathology, the explanation of the phenomenon must lie either in a transient injury caused by the hemoglobin or in some mechanism which is in harmony with the modern concepts of renal function.

The present review, limited to a critical survey of the experimental findings relating to hemoglobinuria, is an attempt to reach a clearer understanding of the factors underlying the elimination of hemoglobin by the kidney.

Numerous histological studies have demonstrated the presence of hemoglobin or its iron-containing breakdown products as granules of varying size in the epithelium of the convoluted tubules, following the intravenous injection of hemoglobin (6, 17, 24, 28). Minute brown granules are observed immediately after the initiation of hemoglobinuria, at which time they do not give a Prussian blue reaction for iron but may be stained by various methods which are specific for hemoglobin (15, 24, 28). After a lapse of several days or following repeated injections of hemoglobin the granules in the epithelial cells of the convoluted tubules appear larger and readily stain for iron (6). Such findings indicate that this portion of the kidney plays some part in the process of hemoglobin elimination and for years a controversy has existed as to whether the tubular activity is one of excretion or reabsorption.

The early exponents of the tubular excretion theory argued on a purely theoretical and inadequate experimental basis that this was the only mechanism involved (31). More recently the question of a dual process of glomerular filtration plus tubular excretion has been advocated by some observers (15, 17). In reviewing this work no definitely positive evidence of tubular excretion can be found and it would seem, in most instances, that an interpretation of the findings, in favor of reabsorption, could equally well be made. Also, evidence derived from the study of lower vertebrate forms indicates that such conclusions probably are not valid. It has been shown that directional movements of granules in epithelial cells cannot be established on histological bases (20, 27), that the aglomerular nephron does not eliminate hemoglobin even after injury with mercuric chloride (5), and that the basilar portions of the renal tubular cells of the toad are impermeable to large negatively charged colloidal molecules (16, 28).

Evidence favoring the belief that the hemoglobin, found in the tubular epithelial cells, has passed through the glomerular membrane and subsequently been picked up from the tubular lumina is more decisive. The more cautious studies of early morphologists led them to conclude that hemoglobin was never found in the tubular epithelium unless it could also be demonstrated in the glomerular capsule (23). Much of the early confusion was doubtless due to the fact that hemoglobin is readily observed in the capsular spaces at the height of hemoglobinuria but is not demonstrable at later stages due to the increased dilution. Further indirect proof of glomerular elimination is given by the fact that hemoglobinuria occurs in dogs in the presence of severe tubular damage caused by mercury poisoning (19), and also by the fact that in the course of a study of induced hemoglobinuria in humans, the rate of excretion of hemoglobin was found to be markedly elevated in cases of known glomerular damage (18). Finally an implication of simple glomerular filtration without consideration of tubular activity has been frequently assumed by workers whose research touches only secondarily upon the mode of hemoglobin excretion (9, 21, 45).

Although it is generally conceded that hemoglobin escapes through the glomerulus there is little agreement regarding the way in which it does so. Since serum albumin with a molecular weight (67,000) approximately the same as hemoglobin (68,800) does not normally appear in the urine, certain investigators have proposed that hemoglobin escapes through the glomerulus only as the result of an induced transient injury (9, 14). It cannot be denied that some increase in glomerular permeability is frequently associated with hemoglobinuria. Variable degrees of albuminuria occurring simultaneously with the excretion of the foreign protein egg white (1, 22) and hemoglobin (18, 35, 40), which in the free state is not a normal constituent of plasma, have been reported. The simultaneous excretion of ferri-ammonium citrate with carboxyhemoglobin (17) and egg albumin (2) has also been adduced as evidence of glomerular injury. The results of these studies are not consistent and since ferri-ammonium citrate may be found normally in the glomerular fluid (20), together with the presence of toxic impurities in many samples of this salt (43), the importance of such a line of investigation tends to be diminished.

A careful evaluation of all the evidence at hand indicates that glomerular injury is not the fundamental mechanism of hemoglobin excretion. Numerous studies have shown that the intravenous injection of carefully prepared, stroma-free hemoglobin solutions had no systemic

pharmacological activity (26, 34, 41) other than a transient, unique, localized renal vasoconstriction (30, 32), and no histological evidence of glomerular damage has been observed in a great mass of material examined (4, 10, 23).

The only evidence of glomerular injury derived from the many physiological studies of hemoglobinuria found in the literature is the simultaneous occurrence of albuminuria. However, the reports of this phenomenon are extremely inconsistent. In some experiments no albuminuria has been encountered, in many there have been slight traces only, while in a few, fairly large quantities have been observed. Marked variations have also been noted in the duration of the albuminuria, from short intervals at the height of hemoglobin excretion to periods lasting for several hours after the cessation of hemoglobinuria (12, 18, 35). The above findings and the relatively small and variable quantities of excess urinary protein encountered in this laboratory in dogs with induced hemoglobinuria are in very marked contrast to the regularity with which hemoglobin is excreted. In dogs and presumably other mammals the rate of hemoglobin excretion above a threshold level is directly proportional to its concentration in the plasma. It is difficult to conceive of any injury phenomenon initiating a mechanism responsible for such a relationship, which has been studied for plasma concentrations up to 1300 mgm. per 100 cc., and which is independent of the initial level of hemoglobinemia induced (32). If, on the other hand, hemoglobin circulating freely in the plasma increases glomerular permeability, it does so in direct proportion to its concentration above a critical level.

The nature of the glomerular membrane must be taken into careful consideration in any speculation about the manner in which a large molecule like hemoglobin may normally pass through it. Anatomically, capillaries in general and those of the glomerulus in particular are considered as having a very thin continuous endothelial lining. The protoplasm of these cells forms the semi-permeable membrane through which water and dissolved electrolytes may diffuse readily, and glomerular filtration pressure is equal to the difference between the hydrostatic pressure of the blood and the colloidal osmotic pressure of the plasma proteins.

Krogh (25) states that substances pass directly through the protoplasm of endothelial cells and also refers to pores in the walls of capillaries, although any mention of whether these are anatomical entities is carefully avoided.

There is apparently a relationship between the diffusion rates of

colloids and their passage through the walls of capillaries; however, it may be argued that this is just a coincidence and that in reality the escape of protein is restricted by the size of the pores in the membrane. The question of increased capillary permeability also presents a serious problem for although many causative factors are known, the nature of the underlying change is still undetermined.

Despite these uncertainties, the modern filtration theory of renal function, for all practical purposes, considers the glomerulus as a purely mechanical sieve containing innumerable pores each large enough to permit the passage of an inulin molecule (molecular weight 15,000). Such a concept indicates only a minimum but not a maximum pore size. The upper limit may be set at a molecular size approximately that of hemoglobin since no substances of higher molecular weight are known to pass through the glomerulus under normal conditions. The presence of a small amount of protein in fluid pipetted from the glomerular capsules of frogs suggested to Richards and Walker (38) that there might be a few pores in the glomerular membrane large enough to allow whole plasma to pass through and an expansion of this idea provides a clue to the possible mechanism of hemoglobin filtration. If actual pores do exist in the glomerular filter, it does not seem necessary to assume that all are of the same size and in fact studies on the excretion of hemoglobin and other proteins of smaller molecular size strongly suggest that gradations do exist. Muscle hemoglobin with a molecular weight of 17,500 (44) is excreted rapidly and has a clearance ratio with creatinine of about 0.58 in the dog (46). Since there is evidence of some tubular reabsorption of this substance its filtration rate has been estimated as about 0.75 times that of creatinine (46). Bayliss, Kerridge and Russell (4) studied the excretion of Bence Jones protein and egg albumin, proteins with estimated molecular weights of about 35,000, from perfused kidneys. No quantitative relative filtration rates are given but the authors state that they are only slightly below that of creatinine. Hemoglobin, at the upper limit, has an estimated filtration ratio with creatinine of only about 0.03 (32). This reflects the very low rate of hemoglobin excretion in relation to its concentration in the plasma and indicates that under maximal conditions only about 3 per cent of the pores in the membrane are large enough to allow a hemoglobin molecule to pass through. This pore size may not be an entirely physical attribute, but one modified by its electro-chemical charge and that of the colloidal molecules in contact with it. Pointing to this possibility are the reversible effects of such surface active sub-

stances as saponin (39) and of variations in pH (45) in modifying glomerular permeability to proteins.

The existence of a renal threshold for hemoglobin was disregarded by most of the earlier workers in the field and even in recent times few who have observed it have hazarded any guess regarding the mechanism involved. It has been implied (26, 35) that the escape of hemoglobin across the glomerulus does not occur unless a certain concentration is present in the plasma and conversely that, after the initiation of a high plasma hemoglobin level, passage of hemoglobin through the glomerulus ceases when hemoglobin ceases to appear in the urine. The dynamic activity which would be required to produce such a "glomerular threshold" is certainly not in harmony with the modern theories of glomerular filtration, for which there is an impressive mass of evidence. Insofar as the excretion of electrolytes is concerned the rôle of the glomerulus is a passive mechanical one, whereas the activity of the tubular epithelium is very highly specialized and selective. This tubular activity is entirely responsible for the renal thresholds of electrolytes so that the assumption of an entirely different mechanism for hemoglobin must be carefully considered, particularly since some type of tubular reabsorption is known to occur. The concept of a "glomerular threshold" was based largely on the ability to lower the initial threshold by about 46 per cent to a fairly constant level by repeated *diminishing* daily injections (26), and the failure to find deposits of iron-staining material in the epithelium of the convoluted tubules following repeated subthreshold doses. The lowered threshold was explained by assuming that the tubular epithelial cells became filled up to such an extent that they would reabsorb no more. It has since been shown (47) that the renal threshold for hemoglobin in relation to plasma concentration may be lowered by 60 per cent or more depending on the size and number of daily injections sufficient to cause gross hemoglobinuria. Since after lowering the threshold to various levels, the excretion rate curves are parallel to those obtained initially, and since under these conditions the estimated tubular reabsorption rate is lowered proportionally, it is not unreasonable to suppose that a complete cessation of tubular reabsorption would entirely eliminate the threshold. The constant level attained with diminishing daily doses in the earlier experiments suggests a state of equilibrium between the amount of hemoglobin reabsorbed by and the amount of hemoglobin products removed from the tubular epithelium daily, rather than a complete cessation of reabsorption. If modification of tubular reabsorption accounts for the lower threshold, the amount

removed daily is apparently quite significant, for when injections of hemoglobin are discontinued, it returns to its initial level within a period of several weeks (26). Such a mechanism could also explain the absence of iron-staining pigment in the kidney following repeated subthreshold injections since the amount picked up would be less than the rate of daily removal from the tubular epithelium.

In this connection it is important that the curves relating the clearance ratios of hemoglobin and creatinine to the plasma concentration of hemoglobin are almost identical in form, though not of course in magnitude, with those for other threshold substances such as glucose (32). This indicates at least a similarity in excretory pattern which implies for hemoglobin a constant though small rate of glomerular filtration, proceeding until the plasma concentration reaches zero, and a rate of tubular reabsorption which at the threshold is at a maximum and equals the amount of hemoglobin escaping into the tubular lumina.

Figure 1 illustrates the type of graphical analysis of experimental data by which quantitative estimates of the glomerular filtration and tubular reabsorption rates of hemoglobin have been made (32). Line *A* represents the actually determined relationship between excretion rate, in terms of milligrams per minute, and the plasma concentration. The parallel line *B* originating at zero is taken to represent the glomerular filtration rate in relation to the plasma concentration if tubular reabsorption, the perpendicular distance between lines *A* and *B*, reaches a maximum at the threshold and remains constant at higher levels.

An average value for the initial rate of tubular reabsorption lies between 2.0 and 3.0 mgm. per minute (32), and values of less than 1.0 mgm. per minute have been obtained after lowering the threshold by about 70 per cent (47).

The data presented by Bogniard and Whipple (6) show clearly that at least some of the iron-containing portions of hemoglobin are stored in the tubular epithelium. They found the iron content of the kidney markedly elevated after multiple intravenous injections of hemoglobin, in amounts sufficient to cause hemoglobinuria. Dense iron-staining deposits of pigment were seen in the convoluted tubular epithelium many weeks after cessation of such injections when the animals were kept in a normal condition, but the pigment disappeared promptly when anemia was produced by bleeding. More recently iron retention by the kidneys has been determined following the injection of hemoglobin containing radioactive iron (47). Single large injections sufficient to initiate plasma concentrations of about 700 mgm. per 100 cc. were given

to dogs that had not previously received any hemoglobin and to those in which the threshold had been markedly lowered by repeated injections. Tubular reabsorption values were estimated from the rate of pick-up obtained by the graphical analysis outlined above and the time required for the disappearance of hemoglobinemia. The animals were subjected to viviperfusion twenty-four hours later and comparisons were made between the above estimates and the actual amounts of radioactive iron

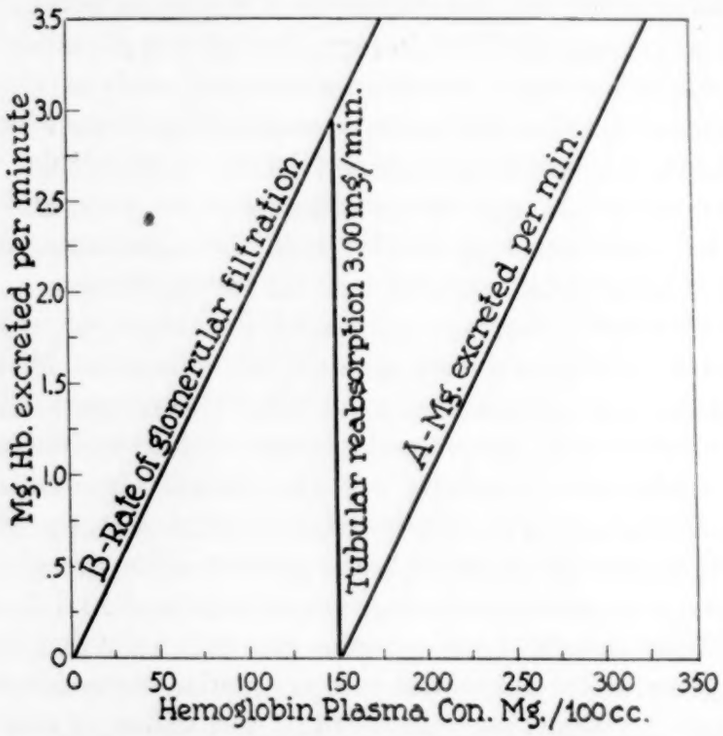

Fig. 1. Graph illustrating the type of analysis of experimental data used to estimate tubular reabsorption. Line *A* represents the actually determined rate of renal hemoglobin excretion above the threshold. The parallel line *B* equals the rate of glomerular filtration if tubular reabsorption, the perpendicular distance between the two lines, reaches a maximum at the threshold and remains constant at higher levels.

found in the kidneys. Calculated values ranged from somewhat over 40 per cent of the injected amount in the normal group to about 20 per cent in the group with thresholds previously lowered by repeated hemoglobin injections. However, only about 16 per cent of the injected iron was present in the kidneys of the normal animals contrasted with over 20 per cent in the kidneys of comparable animals with lowered thresholds. These results cast some doubt on the interpretations originally presented by Monke and Yuile (32), which hold true only if it

is assumed that in normal animals there is a very rapid removal of hemoglobin or its breakdown products from the kidney after it is picked up from the tubular lumina. It must also be assumed that both the intake and output of hemoglobin by the cells of the convoluted tubules are greatly diminished, following repeated injections daily, since under these conditions the amount of iron in the kidneys twenty-four hours after injection equals the total estimate of tubular reabsorption. If the low radioactive iron content of the kidneys in the group of normal animals represents the *total* amount reabsorbed during the entire period of hemoglobinemia, it seems necessary to assume that the glomerulus is responsible, at least in part, for the threshold phenomenon and that it is the permeability of this structure rather than reabsorption by the tubular epithelium which is modified by repeated injections. At the present time much of the evidence favors the theory that tubular reabsorption alone is responsible for the threshold phenomenon but the final proof must await the outcome of further investigations.

Many investigators have estimated the renal threshold level for hemoglobin in man and various animals, but comparisons are often difficult to make. Although a renal threshold for any substance is essentially a function of its plasma concentration, most hemoglobin thresholds have been given as the minimum amount of injected hemoglobin, per kilo of body weight, required to cause hemoglobinuria. This of course will be approximately parallel to the plasma concentration but does not take into consideration variations in plasma volume due to differences in such factors as the state of nutrition or hydration, nor the speed at which the material is injected. Values ranging from 60 mgm. per kilo to about 400 mgm. per kilo have been reported (26, 29, 35, 36, 41). Recent estimations based on more accurate urinary determinations correlated with the plasma concentration of hemoglobin, in a large series of dogs, were found to vary as a rule from about 80 to 150 mgm. per 100 cc. of plasma (32), while in a small group of humans with experimentally induced hemoglobinuria the threshold level was found to lie at about 135 mgm. per 100 cc. (18).

The nature of the process by which hemoglobin, having passed through the glomerulus, is picked up by the epithelium of the convoluted tubules, is apparently quite different from that applying to the movement of glucose and like substances which pass readily from the tubular lumina back into the blood stream.

As previously stated, the tubular epithelial cells exhibit a process of storage and disintegration of the hemoglobin molecule which is not un-

like that seen in the liver, spleen and lymph nodes. Gerard and Cordier (16), in an extensive and careful series of experiments, have studied the mechanism by which various colloidal substances, including hemoglobin, are picked up and stored by the convoluted tubules of the toad (bufo vulgaris, bufo calamita). Their results lend considerable support to the mammalian findings previously outlined. The term "athrocytosis" has been applied to the process by which the tubular epithelial cells form storage granules from ingested colloidal particles. This is a most pronounced phenomenon when studied in the open nephron of the toad. By way of this open nephron, colloidal aggregates of any size can be readily transferred to the unmolested tubular lumen. Microscopical observation reveals that the striated border cells of the proximal segment ingest colloids presented at their apical poles. The cells do so in terms of a molecular size gradient, athrocytosing the smaller colloids in the more proximal portions of the tubule. In the closed nephron this phenomenon is limited to those molecules of near colloidal size which can normally or pathologically pass across the glomerular membrane.

It is interesting to speculate on the manner in which these large colloidal molecules pass into epithelial cells such as those lining the convoluted tubules. Comparison is difficult with the ameboid activity responsible for the phagocytosis of foreign particles by freely wandering histiocytes but the active ingestion of colloidal and particulate matter by the fixed cells lining the sinusoids of the spleen, lymph nodes and liver is perhaps more analogous. In this connection it may be significant that tubular reabsorption of colloids occurs only in that part of the nephron which is mesodermal in origin. This specific problem is linked to the broader one of the passage of large aggregates across cell membranes and the answer may possibly be found in some enzyme activity on the cell surfaces.

Newman and Whipple (33) submit the theory that, in the dog, conservation of hemoglobin is the underlying physiological purpose of tubular reabsorption. The ontogenetic and comparative anatomical studies of Gerard and Crodier (16) justify the application of the same theory to the phenomenon of athrocytosis. The celomic fluid of primitive forms contains quantities of protein solutes, the elimination of which by the open nephron would be a definite loss to the organism. In these lower forms the striated brush border segment functions as an organ of recovery which has become largely vestigial, with the development of a closed nephron.

Although it was originally stated by Drabkin, Widerman and Landow

(13) that about 10 per cent of injected hemoglobin is excreted in the urine, this has been shown to be true only for injections of 100 to 150 mgm. per kilo. Above this level the percentage recovery in the urine increases to as high as 35 to 40 per cent, approximately in proportion to the amount injected (18, 32). It is interesting to note that following the injection of large quantities of hemoglobin much more is removed by renal excretion and retention than was previously thought to be the case.

The foregoing concepts of renal hemoglobin excretion are largely based on quantitative studies in which the urine was rendered and kept alkaline. Under these conditions hemoglobin remains completely in solution during its passage through the kidney and after reaching the bladder. In the presence of acid urine, on the other hand, precipitation within the renal tubules readily occurs causing the formation of casts. The obstruction due to this phenomenon has been thought to be responsible, at least in part, for the fatal anuria which frequently follows transfusions of incompatible blood. However, in view of reports of fatal transfusion reactions with anuria in which little or no hemoglobin was found in the form of casts in the kidneys (11, 12) and the absence of any untoward effects in experimental animals with either acid or alkaline urine from hemoglobinuria induced by the injection of carefully prepared, stroma-free hemoglobin, some discussion of this controversial subject is warranted.

In 1925 Baker and Dodds (3) produced a marked retention of non-protein nitrogen in the blood of rabbits with acid urine by the intravenous injection of hemoglobin but noted no such disturbance when the urine was alkaline. More recently DeNavasquez (12) has injected large doses of hemoglobin into groups of rabbits with both acid and alkaline urine. Some rise in blood urea occurred in either case, but no apparent disturbance in renal function was noted, as judged by phenol red clearance. However, there were marked differences in hemoglobin excretion. Thirty per cent of the injected hemoglobin was recovered in the urine of the acid group as contrasted with only 12 per cent in the alkaline group. On the other hand, the kidneys of the group with alkaline urine retained about 50 per cent more hemoglobin than those of the group in which the urine was acid. Such variations apparently depend on the state of solution of the hemoglobin and the resulting differences in tubular reabsorption.

The carefully controlled experiments of DeGowin, Osterhagen and Andersch (10) show conclusively that although a high percentage of

dogs with strongly acid urine will succumb to transfusions of large amounts of laked red blood cells, death does not occur following similar injections when the urine is alkaline. These experiments do not prove that the precipitation of hemoglobin in the kidney is responsible per se for the observed disturbances, despite the fact that the most striking histological difference between the two groups of animals is the presence of numerous hemoglobin casts in the renal tubules of those with acid urine. Since severe (7) and even fatal (12) transfusion reactions can occur when the urine has been previously alkalinized and remains so throughout, some additional unknown factor, as suggested by DeGowin (11) must be present. Following the transfusion of incompatible blood it is possible that the *foreign protein* of the donor's stroma is responsible for the initial anaphylactoid reaction encountered and the destructive tubular lesions frequently seen in the kidneys. However, this would hardly hold true for the occasional cases of renal failure associated with black water fever and hemoglobinuria due to various drugs. In any event, it is reasonable to assume that the additional precipitation of a large amount of hemoglobin in the tubular lumina will secondarily increase the severity of any reaction.

Since in other types of clinical hemoglobinuria the problems are related to the underlying hemoglobinemia rather than to renal function, they will not be discussed at this time.

Despite the fact that subsequent investigation may modify some of the theoretical concepts here presented, the realization within recent years that hemoglobinuria is a well regulated and reproducible phenomenon should help to clarify much of the earlier confusion relating to this subject.

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THE FUEL FOR MUSCULAR EXERCISE

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There is perhaps no animal texture as to the nature of which more contrary opinions have been held, or more conflicting statements advanced, than that of voluntary muscle, so that even at the present time it must still be considered a question by no means set at rest. (Dobie, 1849.)

The type of metabolites used during muscular contraction has attracted the attention of biochemists and of physiologists for many years. This widespread interest in the problem arises not only from the theoretical implications of this matter but also from its practical application. In spite of the almost universal use of machines, muscular energy developed by man is still a fundamental necessity. It is, therefore, of importance to determine the type of food material used in muscular exercise, the ratio of conversion of energy to useful work provided by various diets, and many other related problems. The limitations of space necessitate exclusion from this review of many interesting problems. Only the following will be discussed: the effect of diet on muscular efficiency and prolonged muscular exertion, the respiratory quotient during exercise, the changes in blood sugar and in blood lactate, and finally, the output of nitrogen in the urine during and after exercise. This discussion will further be limited to experiments done for the most part on man, only an occasional reference being made to results obtained on other animals. No detailed references will be made to the utilization of fat by muscle because this subject has recently been reviewed by Gemmill (1940).

Mechanical efficiency. The mechanical efficiency of men and of animals has been used to determine the character of metabolism during muscular exercise. To the speed and the load, the two chief variables that affect efficiency of muscular work, a third variable may be added, namely, the effect of previous diet on the efficiency. If the different food materials are used in isodynamic equivalents, there will be no change in

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efficiency for either the oxidation of carbohydrate, fat, or protein during the exercise. However, if the body must convert one form into another before it can be used to supply energy to the contracting muscles, there may be loss of energy in this conversion and the mechanical efficiency may be lowered. There have been numerous calculations for the determination of this loss, especially for the conversion of fat to carbohydrate. The calculated results range from endothermic "loss" to exothermic "gain." The various equations postulated for the interconversion of fat to carbohydrate and their thermodynamic possibilities have been reviewed by Rapport (1930). It is obvious that none of the theoretical thermodynamic calculations have any meaning until the exact chemical pathways and the total amounts of material entering into the interchange are known.

Two general methods have been used in this type of experiments. In the first, the subject is given a diet high in one of the primary food materials and low in the others. After several days of such feeding, the subject exercises in the basal condition. The object of these experiments is to saturate the body with one foodstuff and to deplete it of the others. The difficulty of interpreting the results is that food materials are converted into different forms in the body. Proteins, for example, are readily converted to carbohydrate, and carbohydrates are changed to fat.

The second method used in this field is to superimpose exercise on to the specific dynamic action of the food material in question. These experiments are made with the subject exercising after taking a meal rich in the food material under study. These studies are based on the theory that the ingested food material will be used during exercise, an idea not founded on any experimental proof. One of the difficulties in deciding whether there is a difference in efficiency in the latter experiments depends on the base line used in these experiments. The extra metabolism for work is superimposed on the extra metabolism which is due to the ingestion of protein (Anderson and Lusk, 1917; Rapport, 1929), but not on the specific dynamic action of carbohydrate or of fat. This means that in the case of a protein meal the gross efficiency based on the total energy expended may be less after the meal than under basal conditions, whereas the net efficiency based on the extra metabolic activity above the specific dynamic activity may not change. On the other hand, as compared to basal conditions, the gross efficiency may not change when exercise follows a fat or carbohydrate meal, but the net efficiency calculated from the difference between the metabolism during exercise and

just before exercise would give an erroneous idea of the rise in metabolism which was due to the exercise itself. Therefore, in experiments of this type, the best efficiency to use for exercise following a protein meal would be net efficiency; the best following a fat or carbohydrate meal would be the gross efficiency. Although there are many additional difficulties, both theoretical and experimental, in using the mechanical efficiency of man for the determination of the type of food material used by the muscles in exercise, the findings of such experiments are of interest. They demonstrate clearly that there is very little change of muscular efficiency in a subject fed on diets of carbohydrate, fats, or proteins.

There have been numerous determinations of muscular efficiencies made on man in a basal state following diets high in fats, carbohydrates, or proteins. Benedict and Cathcart (1913) report values of 5.37 Calories produced for each Calorie of external work following a carbohydrate rich diet, and 5.31 Calories on a carbohydrate poor diet. Krogh and Lindhard (1920) reported their results in terms of net energy expenditure per unit of work for theoretically determined respiratory quotients. By projecting a straight line through the experimentally determined points, they found the theoretical energy expenditure for respiratory quotients of 1.00 and 0.70. The difference between those theoretical values gave their subjects an average of 11 per cent greater efficiency on a carbohydrate diet than on a fat diet. However, in some of their series it is obvious that there is not a straight line relationship between these two variables (for example, on p. 328, fig. 15); and, therefore, the projection of a straight line through the determined points may give erroneous theoretical values for the Calories used at the respiratory quotients of 0.7 and 1.00. There can be no doubt that their subjects were slightly more efficient on carbohydrate diets, but the order of magnitude may be less than 11 per cent depending on how the line is projected to the ordinates. The work of Krogh and Lindhard was continued in their laboratory by Bierring (1932). His results also leave no doubt that the Calories expended are higher at the lower respiratory quotients, but, again, like Krogh and Lindhard, this author uses a projected line to obtain the two extremes for his calculation. Taking the projected values at respiratory quotients of 1.0 and 0.70, he claims that there is an 8.3 per cent difference in efficiency when fat is used as compared to carbohydrate. As actually determined (fig. 6, p. 39), the highest R.Q. obtained was 0.93 where the work expenditure was 4.6 Calories; the lowest R.Q. was 0.75 where the Caloric output was 4.82. Therefore, the actual difference is 4.5 per cent between these two determined points.

Reynolds, Sevringhaus and Stark (1927) attempted to repeat the ex-

periments of Krogh and Lindhard. Their subjects were not in basal condition as the experiments were conducted 1.5 hours after the noon meal and the subject's only rest before the experiment consisted of sitting 12 to 15 minutes on the ergometer. Records of oxygen consumption were taken from a spirometer which gave oxygen consumption for periods of less than two minutes. Since respiratory quotients were not determined, it is impossible to analyze their results in the same manner as those of Krogh and Lindhard. In some of the experiments the work was very light, for example, in subject M. S. R. only increasing the oxygen consumption to 1254 ml. per min. No attempt was made to keep the work constant as can be seen by the variation in oxygen consumption during work. For example, in subject E. L. S., the oxygen consumption varied from 883 ml. per min. to 2411 ml. per min. They concluded from this experiment that the average net efficiencies on mixed carbohydrate or fat diets did not vary. In view of the conditions under which these experiments were made, their results will not be given any weight in the summary. Marsh and Murlin (1928) have reported net efficiencies of a subject given a normal diet, a high carbohydrate diet, and a high fat diet. The work was very light, only raising the oxygen consumption to 668 ml. per minute. They observed that the net efficiencies on the three diets were about the same, but on continuing the diets there was a decrease in efficiency on the fat diet, especially noticeable after the third or fourth day. The difference between the efficiencies on the carbohydrate and fat diets was of the same order of magnitude as reported by Krogh and Lindhard. Wishart (1934) fed a professional cyclist diets containing varying amount of proteins and found a higher gross efficiency on the lower protein diet, although the subject could pedal for a longer period of time on the higher than the lower protein diet. Even when a correction was made for the specific dynamic action of the protein, the difference between the efficiencies was still clear. In very carefully controlled experiments Cathcart and Burnett (1926) reported a slight decrease in oxygen consumption per kilogram meter of work when the subject was on a carbohydrate diet. The value obtained with the subject on a fat diet was comparable to that observed with the subject on a mixed diet. The most recent experiments in this field are those of Christensen and Hansen (1939) in which the results were obtained under conditions of strenuous muscular exercise. In one individual the net energy production was lower at a R.Q. of 0.78 (11.50 Cal. per min.) than at a R.Q. of 0.92 (11.90 Cal. per min.), but in the other two subjects there was a slight increase in the output of energy on fat diets.

The second method of experimentation in this field, that of feeding

certain food materials before the exercise, has given the same results as the experiments described above in which the experimental subject was in the basal condition after a diet high in one food material. The first thorough study in this field on animals was made by Anderson and Lusk (1917). These authors measured the resting metabolism of a dog under basal conditions and compared it with the excess metabolism of the dog running at a definite rate soon after the ingestion of glucose, meat, or alanine. This type of experimentation does not give the mechanical efficiency of exercise in the true physical sense, but does give comparable values for energy output for performing a definite amount of work. These workers report that it requires 0.580 kilogram meter of energy to move one kilogram of the body weight of a dog one meter with the dog under basal conditions, after a long period of fasting and after meat or alanine ingestion. There was a slight decrease in this value when carbohydrate was given. Following ingestion of 70 grams of glucose, 0.579 and 0.555 kilogram meter per kilogram were expended in two experiments. After taking 100 grams of carbohydrate, a value of 0.550 was obtained. These results demonstrate that the energy expended for running in a dog on a carbohydrate diet is slightly less (5 per cent) than during starvation or on a protein diet. Rapport (1929) extended the observations of Anderson and Lusk by determining the metabolism of running after the ingestion of fat as well as carbohydrate and protein. He found that 2.40 Calories were expended to move 1 kilo of body weight of the dog one meter under basal conditions, 2.38 Calories after ingestion of glucose, 2.54 Calories after the ingestion of fat. These results demonstrate that the energy expenditure after a carbohydrate diet was the same as during the post-absorptive state and was slightly greater after fat ingestion. Rapport also confirmed Anderson and Lusk in their observation that the metabolism during exercise was superimposed on the specific dynamic action of protein.

In man, there have been numerous studies of the effect of ingestion of food on mechanical efficiency. Carpenter and Fox (1931) could not detect any change in net efficiency from the basal level following the ingestion of glucose and fructose when the subject was working at the rate of 275 and 555 kilogram meters per minute. In contrast, Haggard and Greenberg (1935) in their monograph on Diet and Physical Efficiency, give very remarkable changes in the net efficiency of man following a meal. In one individual the efficiency rose from 19.5 per cent to 27 per cent following breakfast. By 12:00 noon it had fallen to 21.2 per cent, but on taking the noon meal it rose to 26.0 per cent. Since eating fat

in the form of olive oil did not change the efficiency, and eating lean beef or glucose did, these authors concluded that protein and carbohydrate in the diet had the ability to increase the efficiency. These experiments were made on a bicycle ergometer, on which the subject pedalled for five minutes. A collection of expired air was made for that period and for a ten minute recovery. The work was light, raising the oxygen consumption to 1500 ml. of oxygen per minute.

These experiments are at variance with others performed in this field. Repetition of these experiments by Haldi, Bachmann, Ensor and Wynn (1938) failed to show any difference in efficiency following the ingestion of glucose, or after breakfast, although there was a rise in the respiratory quotient. Carpenter and Lee (1938) also determined net efficiencies after the ingestion of sucrose and galactose and found only a small change in efficiency. The control experiments, in which 275 kgm. of work per minute was performed, gave values varying from 18.4 to 20.2 per cent; experiments with sucrose gave values ranging from 17 to 20 per cent, but those with galactose showed slightly higher values, 19 to 21 per cent. Increasing the work to 550 kilogram meters per minute after the subject had ingested various sugars, gave values for efficiency higher than in the preceding series. The range was now from 21 to 26 per cent. However, the basal values for the efficiency of these experiments were higher, ranging from 21.9 to 24.7. These experiments show that the ingestion of food material does not change the efficiency of muscular exercise. In light of this work and that of Haldi and his associates, it is impossible to accept the conclusions given by Haggard and Greenberg. The general assumption must be made that ingestion of food material has very little effect on efficiency of muscular exercise.

The conclusion to be drawn from the experiments on the determination of muscular efficiency following various diets is that the efficiency is practically the same on all diets. There is a slight increase in efficiency following a high carbohydrate diet, but probably not more than 5 per cent.

Duration of exercise on different diets. Another approach to the problem has been the determination of the working capacity of man and animals on different diets. In these experiments the end point used is fatigue. In dogs Dill, Edwards and Talbott (1932) have shown that a dog can run 17 hours without exhaustion when given carbohydrate, but without food the dog at its best could do only $4\frac{1}{2}$ hours. By giving carbohydrate to a fatigued dog, the animal was revived and was able to resume work. Unfortunately, in these experiments, other food mate-

rials were not given. The most recent experiments on man in this field are those reported by Christensen and Hansen (1939). Working with an intensity of 1080 kgm. per minute, their subject was able to continue three times as long on a carbohydrate diet as on a fat diet.

Recently it has been claimed that the ingestion of gelatin will enable a man to combat fatigue. Ray, Johnson and Taylor (1939) reported that the taking of 60 grams of gelatin a day increased the length of time that men could ride a stationary bicycle before fatigue set in. In ten subjects, 6 men and 4 women, remarkable increases in work capacity were observed in the men on the gelatin diet but not in the women. Hellebrandt, Rork and Brogdon (1940) repeated this work on a group of women accustomed to severe physical activity. They exercised on a bicycle at such a rate that fatigue set in after 40 seconds of work. The taking of gelatin did not aid in prolonging the work capacity under these conditions. It is doubtful whether the taking of any food material will aid in anaerobic work but only in the maintenance of moderate work for long periods of time. Maison (1940) studied the work capacity for contraction of the extensor digitorum communis before, during and after the ingestion of gelatin and aminoacetic acid. After one year of muscular training, neither of these two substances aided in increasing the working ability of this muscle. This author points out that Ray's subjects were incompletely trained. Robinson and Harmon (1941) have reported recently their studies on the effect of gelatin on training to exhausting work. They found that the ingestion of gelatin had no effect on the oxygen debt nor the speed of running. These experiments should be repeated with determinations similar to those of Wishart who found a prolongation of working capacity on high protein diets. Gelatin may aid prolonged muscular activity indirectly by carbohydrate formation.

Atzler and Lehmann (1937) claimed an increase in the output of work during a diet high in lecithin. The ability for both static and dynamic work increased.

The conclusion drawn from these experiments is that carbohydrate is necessary for long continued muscular work. There is not sufficient evidence at the present time to state that other substances such as gelatin, amino acids or lecithin also have this property.

Respiratory quotient. Another popular approach to this problem has been the determination of the respiratory quotient during work. Although difficult to determine, especially during severe exercise, and difficult to interpret, nevertheless, many determinations have been made of this much abused quotient. Carpenter (1931), in his review of the work

up to 1931, concluded that during light work the respiratory quotient does not change, but with heavier work the respiratory quotient rises and as work is continued, falls. He interpreted these changes as indicating that the same mixture of metabolites is burnt during light muscular work as during rest, that heavy work increased the proportion of carbohydrate used, and that long-continued work diminished the supply of carbohydrate and accentuated the utilization of fat. This problem was reviewed also by Dill (1936) with conclusions similar to those by Carpenter.

The only disturbing factor in these general conclusions is the high respiratory quotients reported by Best, Furusawa and Ridout (1929). These authors reported quotients during mild exercise equal to the basal quotients, reaching unity for moderate exercise, and quotients above unity for strenuous work of short duration. It was obvious from their report that in the experiments after strenuous work complete recoveries were not obtained following the exercise, for recovery periods of only 20 to 50 minutes were used. Even in these determinations the R.Q. for the total metabolism was rarely above 1.00, although values for the excess metabolism as high as 1.65 were reported. These experiments were repeated by Gemmill (1931) using adequate controls. The subjects were first trained to breathe through valves under basal conditions for three hours in order to accustom them to the procedure. In order to obtain basal samples, they slept over night in a comfortable bed beside a treadmill. Following this, they ran for ten seconds on the treadmill at a fast rate and then returned to the bed after the exercise. Thus, the only variable in the experiment was the exercise. Collections were made for three hours after the exercise. In these experiments, the gross respiratory quotients were less than one, and the excess respiratory quotients for the three hour period were 1.10, 0.86, 0.85 and 1.00. This work was again repeated by Solandt and Ridout (1933) but they did not use the extreme precautions observed by Gemmill for obtaining basal conditions. In some of their calculations, these authors used the normal variation in basal metabolism as the basis for a complete recovery period; i.e., when the oxygen consumption and carbon dioxide production returned to these limits it was considered complete. In one subject, the oxygen consumption and carbon dioxide production returned to these limits in one and one-half hours; in the other two, there was a slight increase in oxygen consumption over the basal even after one and one-half hours of recovery. They dismiss this portion of the recovery period as not being due to recovery and claim that recovery is complete in one and one-half hours

after the exercise. Under these conditions the excess R.Q. is above unity. This type of argumentation reduces the excess respiratory quotient to one of definition. If this quotient is defined as the ratio of carbon dioxide produced above the basal control experiments to the oxygen used above similar basal control experiments, one quotient is obtained. If the basal control experiments are used for the carbon dioxide calculation and the post exercise base line (table VI, Solandt and Ridout, 1933) for the oxygen consumption, another "excess quotient" is obtained. It is interesting to note that using the first method several of the excess quotients reported by Solandt and Ridout (table V) are approximately unity for the two and one-half hours' recovery.

Two additional papers have appeared showing that the quotient is less than 1.00 for severe muscular exercise. Dill and his associates (1937) reported quotients between 0.9 to 1.0 when their results were corrected for the shift in carbon dioxide tension at the end of a two hour recovery period. Christensen and Hansen (1939) reported gross quotients of 0.95 with their subjects working at a rate demanding 4.15 liters per minute.

The work of Brand and Krogh (1935) is of interest in this connection. They observed a lowering of the respiratory quotient in rats after a working period, and with this low respiratory quotient there was a new formation of carbohydrate.

The conclusions from this work are that the gross respiratory quotient for muscular work is unity or less than unity. The "excess" respiratory quotient obtained by using the basal level before exercise as a base line is also of that order of magnitude. When other base lines are used such as the post exercise oxygen consumption at an arbitrary time of one and one-half hours after exercise, the "excess" respiratory quotient may be above unity. Since the "excess" respiratory quotient depends on a definition of a base line, this conclusion alone warrants its dismissal. Therefore, the conclusions reached by Carpenter in 1931 still hold for the metabolic events occurring in muscular exercise as revealed by the respiratory quotient determinations. In surveying the work done on the respiratory quotient, the reviewer has reached the additional conclusion that its determination during muscular work has not been worth the time, trouble, and effort put on this phase of the study.

Chemical changes in blood. Another general approach to the problem of the fuel for muscular exercise has been the determination of the changes in concentrations of substances in the blood before, during and after exercise. The concentration of any metabolic substances in the

blood is the resultant of many variables. The main factors are the supply of the substance and its utilization. The latter, in turn, depends upon oxidation and deposition. However, many additional factors besides supply and utilization may change blood composition during exercise. Exercise may cause the blood to become more concentrated, and this, in turn, will affect the concentration of all substances in the blood. The rate of blood flow increases, a phenomenon which changes the rate at which chemical substances reach the tissues. The pH of the blood may change, thus affecting the ratio of ionic concentrations in the blood and causing retention or elimination of base by the kidney. The kidney threshold for blood constituents may change. Capillary permeability may vary in exercise. Therefore, for a change in blood concentration to be significant, it must be very marked. Even when the change is of such magnitude that there is no doubt that it was produced directly by muscular contraction, exact interpretation of the change is difficult. The two following examples, the effect of exercise on the glucose and on the lactate concentrations in the blood, will illustrate these difficulties.

Blood glucose. There have been many studies of the effect of exercise on the glucose level in the blood. These findings fall into three groups: under certain conditions the blood glucose level increases; under others, it remains constant; and under still other conditions of exercise, it falls. An analysis will be given of these results.

Edwards, Richards and Dill (1931) examined the blood glucose of a group of football players before and after a game. Before the game the players and substitutes had normal blood sugar levels, but in the game only the players had elevated glucose levels. In these same players, carrying out exercise under laboratory conditions, there was a decrease in blood sugar. The authors of this paper claim that the elevation was an emotional rise. It is difficult to accept this explanation. The players on the bench are under an emotional strain as well as the men in the game. Nevertheless, their blood sugar levels did not change. In some of the players, the blood sugar level was 180 mgm. per cent fifty minutes after the game was over. This could hardly be a continuation of an "emotional" effect. Other factors besides emotion must play a rôle in this continued rise in blood sugar. Solandt and Ferguson (1932) also report an elevation in the blood glucose level persisting thirty minutes after the subject had run a mile in 5 to 6 minutes. In one subject, the resting level before the race was 119 mgm. per cent, but 30 minutes after the exercise it was 190 mgm. per cent. Dill, Edwards and Mead (1935) reported an increase in blood sugar lasting for eighty minutes in an in-

dividual after working. Thornton and White (1933) give a value of 191 mgm. per cent glucose in a member of the 1933 Cambridge boat race crew 22 minutes after a race ended.

This long continued rise in blood sugar is of such definite character that it is of great interest. Several factors promote the continuous rise: 1, severe but not exhaustive exercise; 2, intermittent exercise; 3, lactate formation. As stated above, the psychological effect of emotion may be omitted as a causative factor. The work of Brouha, Cannon and Dill (1936), if it can be applied to man, rules out the sympathetic nervous system as a cause, for they demonstrated that the blood sugar varied within normal limits in the exercising sympathectomized dog. Since the high blood sugar levels accompany lactate formation, the cardio-vascular and respiratory systems must not be able to supply the muscles with sufficient oxygen during the exercise. The presence of lactate in the blood may be a stimulus for production of glucose from glycogen in the liver. As long as lactate is present, glucose will be formed from the glycogen stores after exercise as well as during exercise.

Light muscular exercise does not change the blood sugar level. Many workers have reported this finding. The most interesting recent papers in this connection are those of Douglas and his associates. They not only studied the blood sugar level, but also evaluated the carbohydrate reserves in the body by determining glucose tolerance curves and by observing the changes in blood sugar following the injection of adrenalin and insulin. In the first paper Courtice and Douglas (1936) reported that after the subject had walked 10 miles at the rate of 4.5 per hour, there was no change in his blood sugar level, but there was a slight decrease in the respiratory quotient. On ingestion of glucose, there was only a slight rise in respiratory quotient and a delay in the increase in blood sugar. The fall in this level was more prolonged after exercise than before. Mills (1938) has confirmed these changes in glucose tolerance after light muscular exercise. Margaria (1939) reports also a marked fall in the respiratory quotient following muscular work a decrease which was not associated with a marked change in blood sugar. These findings were confirmed and extended by Douglas and his associates (1939) in their second paper. The glucose tolerance curve after exercise rises to a greater height than before and was very similar to the curve obtained on a low carbohydrate-high fat diet. Injection of insulin after exercise showed no evidence of any change in sensitivity to this hormone. In a third paper Douglas and his associates studied (1939) the effect of adrenalin on the blood sugar of a subject after light

muscular work on a bicycle ergometer. The working period was from 2½ to 3 hours. Comparison of these experiments with the resting experiments showed that the rise in blood sugar concentration following the injection of adrenalin is less and recovery more rapid during work than during rest. These experiments of Douglas and his associates demonstrate that the carbohydrate stores of the body are depleted although the blood sugar does not fall during light muscular exercise. Similar experiments should be carried out in individuals who have worked to a degree when their blood sugar level is actually lowered, in order to see how their carbohydrate stores would function under the action of insulin and adrenalin.

Long continued exercise decreases the blood glucose level. Levine, Gordon and Derick (1924) and Best (1930) reported this result for runners following the Marathon. One interesting finding was that the men with the most marked signs of physical exhaustion had the lowest blood sugar levels. The blood sugar level also falls in men running for long periods on a treadmill (Edwards, Margaria and Dill, 1934).

Strandell (1934) has carried out a series of observations in which glucose was injected just before exercise. If the exercise was severe, the blood glucose did not change; however, during slight exercise, there was an increase in blood sugar. These changes were not due to deficient absorption of the glucose from the digestive tracts. These experiments also indicate that glucose is used by the contracting muscles under severe conditions.

The lowering of the blood glucose level during long continued exercise denotes a marked utilization of carbohydrate for muscular exercise. The rise during and after severe exercise of short duration indicates that the mechanism of supply overbalances the mechanism of utilization. Since the rise accompanies lactate formation, it is suggested that lactate may be the stimulus for the production of glucose from glycogen in the liver under these conditions. In moderate exercise of short duration, the level of blood glucose does not change. It may be assumed that the blood glucose is being used, but in these cases the supply meets the demand.

Lactate. Another substance which has been studied extensively in the blood during and after exercise is lactate. Although analyzed and reported as lactic acid, there is very little lactic acid in the blood, since at the normal pH of the blood this substance is in its ionized form, the lactate ion. Therefore, in this review, the term "lactate" will be used to describe this substance.

Although it was known for some time before the work of Hill and his associates that lactate was formed in the body of man during severe muscular exercise, it was through the efforts of these observers that a possible relationship between speed of working, lactate formation, and duration of recovery period was established. Hill and his associates (1923) postulated that there was a direct relationship between the oxygen used above the base line after exercise and the lactate concentration in the body. They assumed that all of the extra oxygen consumed during the recovery period was due to oxidation of lactate. Hill calculated that an oxygen diet of one liter represented in the body the presence of 8.1 grams of lactate at the end of exercise. Hill and his associates also assumed that even moderate effort increased the lactate concentration in the blood. Long (1926) offered an example of this theory in describing an increase in lactate in the blood of individuals walking at the rate of 3.3 miles per hour. Experimental work during the past ten years has modified these views. Owles (1930) described a critical metabolic level during exercise of varying degrees of severity. At moderate degrees of exercise, there was no increase in lactate in the blood; at more severe grades, lactate accumulated. A more detailed account of the relationship of severity of exercise to lactate production was published by Margaria, Edwards and Dill (1933). These authors described experiments in which blood was drawn from the femoral artery and vein as well as from an arm vein, at various times after exercise. The values for lactate concentration in these various samples were compared to the oxygen debt. The usual difficulty in determining exactly the duration of this debt was encountered, as is evident from their observation that the oxygen consumption in their individual was 30 ml. per minute above the basal level even two hours after work had stopped. This increment they disregarded in their determinations, and took instead an arbitrary value of one and one-half hours for their recovery periods. Their results show clearly that there was no lactate appearing in the blood for oxygen debts up to 3.0 liters per minute. Above this value, there was a straight line relationship between lactate concentration and oxygen debt. These authors conclude that there are two phases to the recovery period, an alactacid debt which does not depend on lactate production and a lactacid debt which is related to the oxidation of lactate. Cook and Hurst (1933), at the time of publication of Dill's work, showed that the exercise of walking at the rate of 4.5 miles per hour for 30 minutes did not change the concentration of lactate in the blood of the femoral vein. These authors also report the interesting comparison of lactate concen-

tration in arterial and venous bloods following running to complete fatigue in 1 minute. In two subjects from whose femoral arteries and veins simultaneous blood samples were taken 3 minutes after the exercise, the venous lactate concentration was greater than the arterial; in the third subject, from whom the blood was obtained five minutes after exercise, this condition was reversed.

The work on the relationship between oxygen debt and lactate production was continued by Margaria and Edwards (1934). They demonstrated that there was not a rapid removal of lactate at the beginning of recovery corresponding to the rapid fall in oxygen consumption. Therefore, there was a delay in lactate removal. They also observed a curious fact that the speed of removal of lactate in man is inversely proportional to the amount of lactate formed. This work was repeated later by Newman, Dill, Edwards and Webster (1937). They did the clever experiment of having the subject run to exhaustion in order to saturate the body with lactate and then have the subject exercise at a more moderate rate. The rate of disappearance of lactate under these conditions was faster than during rest, and, in fact, was greater with more severe grades of the exercise in the second period. These authors list the following conditions as possibilities for explaining the removal of lactate: loss in sweat and urine, utilization by heart muscle, utilization by active skeletal muscle for fuel, and the more rapid circulatory rate. Bang (1936) has also described a decrease in lactate concentration in the blood during work. In his cases, the slope of the decrease is approximately the same as during a resting recovery period. If the work is continued long enough, the values at the end of the exercise may be the same as the basal level, demonstrating that a full recovery to the basal level may take place during exercise. However, when the exercise is severe, a secondary rise is obtained during the exercise. These changes in lactate concentration are accompanied by small changes in pyruvate concentration (Johnson and Edwards, 1937) and are not affected by the removal of the sympathetic nervous system in dogs (Edwards, Brouha and Johnson, 1938).

In all of this work, the assumption was made that the lactate in a sample of blood is in equilibrium with the lactate in the tissues. Unfortunately, direct determination of the lactate concentration in the tissues and blood has not always shown this to be true. Margaria and Edwards (1934) studied the rate of disappearance of lactate from the whole body of mice following a period of muscular stimulation. The mice were dropped into a freezing mixture, and the total lactate determined. Since

the rate of disappearance of lactate from the body of the mouse corresponded to the same slope for disappearance of lactate in the blood of man, they concluded that the blood lactate concentration represented body lactate concentration. Sacks and Sacks (1937) approached the problem more directly by comparing the lactate concentration of a cat's stimulated muscle with that of venous blood. They report marked differences between these concentrations: for example, the muscle had 324 mgm. per cent lactate while the blood only had 59 mgm. per cent. Even after two minutes of recovery, there was still a wide difference between the concentrations in muscle and blood. When these experiments were repeated in rabbits, closer correlation was observed than in cats. Newman (1938) studied the lactate concentration in the blood of rats and in the working muscles. He reports good agreement between these two variables up to increments of 80 mgm. per cent. Bang (1936) agrees with Sacks and Sacks that there is an unequal distribution of lactate between blood and tissues.

It is difficult for the reviewer to understand why there should be a marked difference between the lactate in the muscle and in the venous blood. The rate of diffusion of lactate from isolated muscle is a function of the amount present. Eggleton, Eggleton and Hill (1928) suggested that the diffusion takes place through the lymph interspaces, where diffusion is rapid, and through the muscle fibers, where diffusion is 100 times slower. The net diffusion rate depends on these two variables. In a fatigued muscle, the muscle fibers may swell, causing the lymph spaces to decrease, and thus impede diffusion. It may be that these changes are more pronounced in the cat than in mice, rabbits and rats. It may also be that the circulation through the muscle of the cat is less efficient than in the other species. It would be of interest to compare the capillary bed of a stimulated cat's muscle with that of a dog or rat. It is well known that a cat has very little capacity for long continued exercise. Hodes (1939) reports that a cat could run for four minutes on a circular treadmill without noticeable ill effects. A calculation from his data gives the rate at approximately 3 miles per hour. This is in marked contrast to a dog which will go for 17 hours at this rate without noticeable ill effects on the output of work. It is very possible that the circulatory and diffusion factors in the cat may be different from those in the dog and rat. Unfortunately no information is available on this important point for man.

The lactate that appears in the blood is connected with the anaerobic mechanisms in the muscle, a fact which is obvious in very severe grades

of muscular work in which the supply of oxygen does not meet the demand. It is not so obvious for light grades of muscular work. Sacks, Sacks and Shaw (1937) report that at the beginning of stimulation of a muscle, there is always a slight increment in lactate formation which is not increased by continued stimulation. Flock, Ingle and Bollman (1939) have also made a similar finding. Therefore, the beginning of muscular exercise is also an anaerobic condition, since the circulatory and respiratory adjustments require a short period of time before they reach sufficient capacity to carry oxygen to the muscles to meet the new demands. This separation between the aerobic and anaerobic phases in muscular energetics has been reviewed elsewhere (Gemmill, 1939; Sacks, 1941). Since the lactate comes from carbohydrate, carbohydrate is of importance in the early phases of muscular contraction as well as in the prolongation of muscular work.

Excretion of nitrogen in urine. A method which has been used extensively for the determination of the rôle of protein in the metabolic changes during muscular activity has been to measure the nitrogen output in the urine before, during and after exercise. Cathcart (1925), in his review, concluded that the small increment in nitrogen excretion observed during exercise did signify that protein was used as a fuel for muscular work. He discussed the complexity of the problem and suggested that protein might be retained during exercise, inasmuch as the work hypertrophy of muscle would need additional protein. Therefore, the true utilization for muscular work would be masked by the synthetic utilization of the nitrogen-containing residues of protein metabolism.

There are many factors which may change the output of a substance in the urine during and following work, besides an actual increase in the amount of this substance formed by the body. Kidney function may be affected by exercise. Grande and Rehberg (1936) report that light work does not affect kidney function, but heavy work produces signs of renal insufficiency. Hellebrandt, Brogdon and Kelso (1932) described an albuminuria produced by prolonged steady work as well as rapid and exhausting work. These authors advance the idea that the increase in acidity changes the permeability of the renal tissues to proteins. Edwards, Richards and Dill (1931) also have described albuminuria following exercise. If exercise may bring about a change in permeability of the renal tissues to proteins, the output of many other substances may also be affected. Therefore, in evaluating nitrogen output experiments, more significance should be attached to the output for long periods after the exercise than for short periods immediately following exercise.

The fact that exercise increases the output of nitrogen has been confirmed by several observers since Cathcart (1925) wrote his review. His own careful studies with Burnett (1926) demonstrated that exercise increases nitrogen excretion and that there is a parallel increase in sulphur output. Garry (1927) studied the output of nitrogen during static work by allowing the subject to pull against heavy springs and to hold weights suspended by a foot lever. A tremor developed in the contracting muscles which became progressively worse during the time of the experiment. This type of work produced a small rise in the output of total nitrogen, the general average, changing from 15.12 grams per day before the exercise, to 15.77 grams on the day of the exercise, then increasing to 16.36 grams on the first day after exercise, and not falling back to the basal level until three days after the experiment. Wilson (1932), whose subject carried out work on a hand or bicycle ergometer, demonstrated a definite rise in nitrogen output followed by a secondary fall. The work done by his subjects varied from 22,000 to 34,000 kilogram meters per day, and the work periods extended from 4 to 18 days. However, the changes in the excretion of nitrogen and sulfur did not parallel the amount of work done which indicates that there is no direct relationship between these two variables. Later (1934) Wilson reported results of an experiment in which a cyclist rode a bicycle ergometer for 8 hours doing up to 366,850 kilogram meters of work in the day. Again, an increase in the output of nitrogen occurred on the working day followed by a fall below the basal level on the third day after the exercise. The subject carried out the work with diets containing various amounts of proteins. The greatest absolute increase was obtained when the diet was highest in protein. Cuthbertson, McGirr and Munro (1937) have described a nitrogen sparing action of carbohydrate on protein metabolism during exercise. If a meal of carbohydrate is ingested before the work, the rise in nitrogen and sulfur in the urine following work does not occur. These experiments are of special interest, for they indicate a possible explanation for the rise in nitrogen in the urine during and after work. In long continued work, the carbohydrate supply is exhausted, and extra protein is converted into carbohydrate or carbohydrate intermediates to supply energy. This fact would explain the long continued output of nitrogen after exercise. It may also explain the long continued increase in oxygen consumption after work. Herxheimer, Wissing and Wolff (1926) have found an increase of 10 per cent above the basal level even 36 to 48 hours after work. Edwards, Thorndike and Dill (1935) have described a 25 per cent rise above the basal

level 15 hours after activity. A continued oxidative deamination of amino acids would produce these changes in oxygen consumption.

The conclusions to be drawn from this work are that long continued muscular exercise produces an increase in the output of nitrogen in the urine. Since the severity of the work does not affect the output, there is no direct relationship between exercise and nitrogen output. An indirect relationship is postulated; exercise reduces the carbohydrate supply of the body, extra protein is deaminized to supply carbohydrate or carbohydrate intermediates. The evidence for this assumption is based on the fact that ingestion of carbohydrate abolishes the increment of nitrogen output. This idea may also explain the long recovery period observed by some authors.

GENERAL SUMMARY

From the survey of the literature it is obvious that the use of carbohydrate is of primary importance as a fuel for muscular exercise in man. The evidence comes from the slight increase in efficiency on a carbohydrate diet, the prolongation of muscular effort when carbohydrate is ingested, the fall in blood sugar during long continued muscular exercise and the production of lactate at the beginning of exercise and during severe exercise. The evidence that protein is used during exercise indicates that it is of secondary importance, probably to supply carbohydrate or carbohydrate intermediates. The results of experiments on fat utilization during muscular work have demonstrated that this substance is used indirectly. There is no experimental evidence at the present time for the direct utilization of fat by mammalian muscle. However, the indirect utilization of protein or fat must be an efficient process, since the exclusive feeding of these substances to man does not have a marked effect on muscular efficiency during short periods of exercise.

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RECENT ADVANCES IN KNOWLEDGE OF THE LIVER[1]

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Rather than attempt a complete review of the extensive recent literature, the author in the present article desires to piece together an account of some of the more important of the newer contributions toward our understanding of the liver's physiology. The pathology will hardly be touched upon and many topics will be referred to merely with brief mention of the literature. Recent reviews not quoted in the text are: Greene (1941), Hawkins (1931), Ivy and Crandall (1941), Josephson (1941), Mann and Bollman (1939).

The rôle played by the liver in the maintenance of blood levels of sugar, urea and protein. From the time of Bernard's discoveries in the 1850's physiologists have investigated the nature of the liver's control of carbohydrate metabolism, but much of the evidence gained was conflicting and confusing. The cause of this is now clear. For one thing it was unknown that various hormones and enzymes, activators and the like were taking part in the liver's activities. The gradual discovery of these and their interactions, the rise of the concepts that the blood-level of a substance of itself releases regulating mechanisms, and of a balanced endocrine action, finally explained many conflicting observations. Another important advance was the gradual perfecting of methods and techniques whereby the physiological integrity of the liverless animal could be maintained for periods long enough to allow one to make a satisfactory series of observations. This was done by F. C. Mann (1921) who finally with associates (1925) established beyond all doubt that the liver is the chief organ concerned with the maintenance of the blood-sugar level; their method was extended and their results confirmed by Soskin and his associates (1927; see review of the literature by Soskin, 1941).

But with all our advances the complete pattern of the mechanism of the extrinsic control of the liver carbohydrate metabolism cannot yet be

[1] Supported in part by a grant from the Rockefeller Foundation Fluid Research Fund.

outlined. For example, from Professor Fiessinger's laboratory in Paris comes a dissertation (Bareillier-Fouché, 1939) reporting what appears to be careful work and convincing evidence that insulin injected into the portal bloodstream of the isolated, perfused cat's liver increases the output of sugar in the hepatic outflow: a veritable hyperglycemia is produced. On the other hand de Bodo and his co-workers, making their observations with the organ *in situ*, show that liver-glycogen mobilization occurs in the absence of adrenal medulla and liver nerves (1938), that in the absence of anterior pituitary liver-glycogen is not readily mobilized by adrenalin (1941a), and that insulin given in doses too small to evoke a more than slight drop in blood sugar in normal dogs, will produce a hypoglycemic shock in completely hypophysectomized dogs. From these observations they conclude that the factors normally effective in mobilizing liver glycogen are ineffective in the absence of the anterior pituitary, hence the sensitivity to insulin observed in hypophysectomized animals (1941b). The findings of de Bodo and his colleagues are supported in part by the independent observations of A. Allen *et al.* (1941) who made their studies upon rats.

Jensen and Grattan (1940) reported evidence that the anti-insulin effect of the anterior pituitary in normal mice may be attributed to the adrenotropic principle of the gland which is mediated through the adrenal cortex. Grattan and Jensen (1940) among others then found the specific principle of the adrenal cortex, which responds to the adrenocorticotropic substance. They suggested that the anti-insulin effect thus produced is probably due to the ability of these substances to promote formation of liver glycogen. Hartman *et al.* (1940) came to a similar conclusion from studies on normal, fasted mice. Grattan *et al.* (1941) show that the adrenotropic factor of the anterior pituitary fails to produce an anti-insulin effect (and to promote glycogenesis) in adrenalectomized mice, but that under the same condition the administration of corticosterone protects them against insulin hypoglycemia and liver glycogenesis.

Corey and Britton (1941) find that isolated cat livers perfused with Ringer-gum-glucose solution, to which cortico-adrenal extract had been added, show greater increases in glycogen content than when other perfusates are used, the average increase being 60 per cent. On the other hand no glycogenesis could be demonstrated in these cat livers when insulin was added to the perfusate, on the contrary a decrease of glycogen content of about 30 per cent was observed. This latter observation agrees with the findings of Bareillier-Fouché (1939) mentioned above,

if the glycogen disappeared as blood-sugar. Working with the liver *in situ*, Britton and Corey (1941) show that extracts of the adrenal cortex, when given with infusions of glucose solutions, will cause large increases in both blood-glucose and glycogen-content of liver and muscle in adrenalectomized cats, whereas insulin will cause no such increases. The adrenalectomized animals when untreated show severe losses in blood-glucose, liver- and muscle-glycogen. On the other hand pancreatectomized animals when untreated show practically normal amounts of liver- and muscle-glycogen and are able to form liver-glycogen from glucose solution alone; the muscle-glycogenesis is facilitated somewhat more with insulin, the liver-glycogenesis somewhat more with cortico-adrenal extract. Cortico-adrenal extracts given with glucose to adreno-pancreatectomized animals relieves them of severe symptoms, prolongs life and even brings about large deposits of glycogen in the liver and cardiac tissues.

From the foregoing and their antecedent data the author has tried to chart the rôle of each hormone acting alone and then in succession with one or more of all the other known effective hormones but there still remain too many conflicts and uncertainties. Further research on both the organ *in situ* and the organ surviving and isolated will be required to fill in all the questions still unanswered.

Protein metabolism. By the use of the Eck-fistula Whipple *et al.* (1937) settled the uncertainty as to the source of blood-plasma protein; among others they were able to show that the liver elaborates and maintains blood-plasma albumin. The literature on this topic has been reviewed by Madden and Whipple (1940).

While von Schröder (1878) showed that the liver is at least the chief, if not the only site for the formation of urea, not until the present decade was it shown, by Krebs and Henseleit (1932), that, of the rat's body, liver is the only tissue (when studied in slices by Warburg technique) that is able to synthesize urea. Finally Bollman and Mann (1933) demonstrated that no urea at all is formed in liverless dogs. We conclude now that the liver is the sole seat of urea formation in the mammalian body, a conclusion that is fully confirmed by the studies of Maddock *et al.* (1938) and Svedberg *et al.* (1938) who followed the nitrogenous metabolism in hepato-nephrectomized monkeys and rabbits respectively.

Knowledge of the metabolic interrelations between the liver and such substances as the phosphatids, lecithin and choline is gaining by leaps and bounds. For recent reviews one may consult Best and Ridout (1939), King (1939), Channon (1940).

Elements controlling blood coagulation. It is known also that the liver is the only source of fibrinogen (Foster and Whipple, 1922) and of prothrombin. Further corroboration of the fact that the liver elaborates these substances is just now at hand: Brinkhaus and Walker (1941) have shown that the content of liver lymph in prothrombin and fibrinogen is equal to that of blood plasma, while that of femoral lymph is only $\frac{1}{10}$ of that of the blood plasma. Hence the use of the blood level of these substances, as a basis in methods for the estimation of hepatic dysfunction, may be considered well founded.

Heparin was first extracted in Howell's laboratory chiefly from liver, hence its name (McLean, 1916; Howell and Holt, 1918). But recent researches have shown that heparin is produced and stored specifically in the mast-cells, which are scattered generally along the walls of smaller blood vessels and especially along the walls of veins and in the intercapillary spaces. While Glisson's capsule, enclosing the liver lobules, is especially rich in these cells, the lung tissue per unit weight is richer in mast-cells than liver tissue, and therefore is a better source of heparin than whole liver (see Jorpes and Bergström, 1936; Holmgren and Wilander, 1937). We can see now that while small injuries to tissues would tend to the release of the clot-promoting thromboplastic substance and thus to the formation of clots, the presence of the mast-cells in such cases may lead somehow also to release of heparin, thus preventing clots from forming in the capillaries of minute, circumscribed areas. On the other hand large wounds in muscle masses, where mast-cells are scarce, release amounts of thromboplastin in great excess of the heparin liberated and thus clotting in those cases is insured.

It has long been known that, when dogs are thrown into shock by Witte's peptone, the clotting time of the animal's blood is markedly increased. The nature of this phenomenon was cleared up by Wilander (1938) who showed that the heparin content of the blood of peptone-dogs had increased enough to account for the delayed clotting time and that the mast-cells of their livers had emptied themselves of almost all their stores of metachromatic, granular material, which on account of its special affinity for toluidine blue is believed to be heparin itself. (See also Jorpes, 1939.)

Jacques, Charles and Best (1938) finally have shown that the outflow from the hepatic veins of dogs in anaphylactic shock contains liberated heparin, and that, although dogs without livers can also be thrown into anaphylactic shock, their vena caval blood no longer contains heparin and its clotting time is not increased. They believe therefore that the mast-cells of the liver are the source of the heparin found in the non-

hepatectomized peptone-dogs. Why there is this specific action between Witte's peptone and the mast-cells only of the liver is a problem awaiting solution. (For confirmative evidence see Jacques and Waters, 1941.)

Calder and Kerby (1940) studying patients suffering from certain diseases which develop hemorrhagic syndromes found that intravenous injections of comparatively small amounts of nicotinic acid will remove the hemorrhagic symptoms as well as a number of other pathological conditions. In an attempt to solve the nature of this action of nicotinic acid, by working with samples of the blood of these patients in test tubes, they found that, unlike in the human body, it took enormous doses to shorten the clotting time to a normal period. The authors inferred from this that the rôle of nicotinic acid is probably a pharmacodynamic one, in which minute doses of the drug act first upon the liver causing it to produce and liberate relatively large quantities of prothrombin, or much less antithrombin, and thus to enable the shed blood to clot. This hypothesis should be tested by experiments on the isolated surviving liver.

Vitamins. Nicotinic acid is a substance grouped with the water-soluble B complex of vitamins, and sometimes referred to as vitamin-pp. We come thus to a consideration of the rôle played by the liver in the storage, distribution and activity of vitamins in general.

About sixty-four years ago Boll observed that the pigment in the retina, visual purple, was photosensitive. A year later Kühne discovered that this pigment could be dissolved out from the retina by a solution of bile salts. Following this discovery the power of the eye to adapt itself to vision under dim illumination was ascribed to some hidden chemical reaction of this photosensitive substance. But the first insight into the substances involved in this chemical reaction has been revealed only during recent years.

Beginning with the work of Fredericia and Holm (1925) and culminating in that of Wald and his associates, it has been shown that visual purple is generated in the dark by a synthesis of vitamin A and a carotenoid substance called "retinene," and that the bleaching of the pigment upon exposure to the light is due to a breaking down of this vitamin A-carotenoid combination.[2] If now the quantity of vitamin A in the body begins to fail, the resynthesis of visual purple also begins to fail and thus fails also the power to see in dim light (see Wald, 1935).

[2] There may be doubt as to the exact chemical nature of this dependence. Krause and Sidwell (1938) could not demonstrate that vitamin A is formed by the photochemical reaction of visual purple or visual yellow. That some fundamental relation obtains however is beyond all question.

In 1932 Drummond and others were able to show that the absorption of fat-soluble carotene by the gut could only be carried out if bile acids were present. These authors assumed that the bile acid formed a water-soluble, diffusible compound with the carotene, the absorption and transport of which into the bloodstream was thereby facilitated. Later Drummond *et al.* (1934, 1935) showed that the distribution of fat and vitamin A in the three lobes of the rat's liver is reasonably uniform; that carotene in certain form injected into the portal circulation is rapidly taken up by the Kupfer cells, and when thus taken up tends to disappear within the next few days. No correlation with vitamin A was found at that time but other experiments showed that the removal of one lobe of the liver of itself brings about a loss of vitamin A in the remaining lobes.

Young and Wald (1940) now find that removal of one lobe of the rabbit liver reduces vitamin-A 25 per cent and carotene 50 per cent in the remainder of the organ, while blood-vitamin-A rises 3 to 7.5 times its former values. These authors further find that electrical stimulation of the splanchnic nerves increases blood vitamin-A, while electrical stimulation of the cervical sympathetics has no effect. Schneider and Widman (1934) demonstrated that thyreotropic hormone plays an important part in the cleavage of carotene into vitamin-A and finally causes a discharge of vitamin-A from the liver. Young and Wald conclude that the liver is not only a store-house for vitamin-A but also that its mobilization is affected in ways similar to those which mobilize sugar in the liver.

From these experiments it appears that bile acid, in its rôle as an agent promoting fat resorption, as one would expect, also promotes the resorption of fat-soluble substances. Thus, defects in the liver, leading to a paucity of bile acids in the gut, will lead to a deficiency of carotene and vitamin-A in the blood, which in turn leads to further depletion of stores of these essential substances in the liver and finally to a reduction of their blood-levels.

One recalls that Moll *et al.* (1933) produced a concentrate from fish liver oils very high in vitamin-A, which they called "Vogan." Domagk *et al.* (1933) observed that the Kupfer cells of the liver show a selectivity for fat and that these cells seem primarily concerned with vitamin-A storage and destruction. Vitamin-A given with fats is more easily absorbed and assimilated. But when vitamin-A is given in overdoses *a*, according to Domagk (1933) lipemia follows, and *b*, according to Lasch (1934) serum-cholesterin increases, both due mainly to liver action.

Since the chief natural source of the fat-soluble, antirachitic vitamin-D is in the oils of fish livers the question pertinent in the present inquiry is, why is this vitamin not stored also in the livers of mammals. The answer is that the lung tissue of mammals contains an enzyme which destroys vitamin-D; this depletes the blood and finally the liver and other tissues of lung-breathers of their stores and prevents accumulation of vitamin-D. The gill-breathing fishes on the other hand have no such enzyme; their liver fats therefore are able to accumulate stores of this fat-soluble vitamin. The vitamin-D series is composed of definite sterins which are fats and thus will be taken up by other fats in greater quantity, especially in such livers as store fats instead of carbohydrates. A consideration of the inactive provitamin of vitamin-D and the effect of irradiation upon it, and of the source of the active vitamin in cod livers (they themselves contain mere traces of the provitamin) would take us too far a-field at this time.

Perosis, known otherwise as "slipped tendon" or "hock disease" appearing in chicks, is reported by Hogan *et al.* (1940) to be due to the lack of a factor, which they call B_p, in addition to the lack of manganese in the diet. According to Stepp *et al.* (1938), water-soluble B_1, vitamin-B_2-complex and B_6 are stored up or elaborated, or both, by the liver more than by any other organ. From the experiments of György and Goldblatt (1939) it is known that rats fed on basic rations lacking the "rat growth factor," B_w, develop pathological changes in their livers, which latter can be prevented by adding yeast or yeast extract to the diet. The "chick antidermatitis factor," the "rat growth factor" and "pantothenic acid" probably all belong to one group of substances somehow closely related.

The chromotrichia factor for rat and the growth-promoting factor for chick derived from yeast are identical, if one accepts the work of Ansbacher (1941) and others, and is a vitamin of definitely known composition, namely, p-aminobenzoic acid. This aromatic compound is greatly facilitated in its resorption by the intestine in the presence of bile salts.

Recently Rich and Hamilton (1940) have been able to produce experimentally a form of Laenec's cirrhosis of the liver in normal rabbits by feeding a diet in every respect apparently quite adequate and including the isolated yeast-factors, B_1, B_2, and B_6 or nicotinic acid. But if *full yeast* is added to the diet, the animals no longer develop the cirrhosis. It was therefore concluded that yeast contains as yet some undetermined factor which plays the rôle of an anticirrhotic agent. Maschella and Macguire (1941) could not confirm this. But György and Goldblatt

(1941) report increased incidence of necrotic and cirrhotic lesions in the livers of rats when the normal diet, containing 18 per cent casein, was reduced to one containing 10 per cent and in which lard was substituted for butter. Cystin added to this latter diet increases the incidence; choline added to it, decreases the incidence of the liver injuries. These observations agree with the extensive work of Blumberg and McCollum (1941) who with high fat, low protein diets produced cirrhosis in more than 30 rats and have prevented cirrhosis in a like number of animals by the addition of choline.

Similarly Miller *et al.* (1941) find that rats on a given carcinogenous (butter fat) diet within four months show a 90 to 100 per cent incidence of hepatic tumors which can be reduced by simply increasing the casein or other protein content of the diet. Addition of whole dried brewers' yeast to the carcinogenous diet offered only partial protection. They conclude that the protective elements in such diets are high content of both protein and vitamin-B complex.

From numerous recent public lectures, published reports and reviews (by Dam, 1940; Almquist, 1941; Doisy *et al.*, 1941) it is now well known that several forms of hemorrhagic diatheses are due primarily to lack of a special substance called vitamin-K. The natural vitamin-K is a fat-soluble compound and therefore requires bile acid for its absorption. But Doisy *et al.* have synthesized a quinoid compound in which naphthaquinone is joined to phthiocol. This compound has all the essential characteristics of vitamin-K, but is water-soluble. The point of interest for us at the moment is that K-avitaminosis patients bleed because a clotting factor is absent in their blood. Whipple (1912) had shown that infants suffering from *icterus gravis* had blood of long clotting time. Only in recent years however has it been found that in these cases the immediate trouble is lack of prothrombin. Later studies showed that Vitamin-K normally stimulates the liver to liberate prothrombin into the blood-stream, whereupon the bleeding promptly ceases.

But a third important factor had to be revealed for the final solution of the etiology of these hemorrhagic diseases. If the bile is absent or deficient in the intestine, as in gall-duct obstruction, sufficient vitamin-K is not absorbed. And if, as in the case of the new-born infant, where the diet lacks the vitamin, and the normal intestinal flora do not develop soon enough to provide it, no vitamin-K is at all available, hence the lack of prothrombin in the blood. This explains how, in both these categories of cases, hemorrhagic symptoms develop. By introducing vitamin-K directly into the blood, or better by intramuscular injection,

one has an effective procedure which makes the patient safe from bleedings occasioned by trauma or surgical intervention until he can normally supply sufficient quantities of the vitamin from his own alimentation. The mechanism whereby vitamin-K is able to stimulate the liver to produce prothrombin is still to be solved.

Miscellaneous. Depancreatized animals treated with insulin under certain conditions commonly develop marked hypolipemia and fatty infiltration of the liver. To test out the idea that this change in fat metabolism may be attributed to lipocaic deficiency (Dragstedt *et al.*, 1936), or to defective digestion and absorption of fats (due to absence of pancreatic juice in the intestine) J. G. Allen *et al.* (1941), having made complete external deviations of the pancreatic juice in dogs, found in these cases that the blood and liver lipoids nevertheless remain within the normal range. It would appear here then that the bile even in the absence of pancreatic juice still plays an important rôle in fat absorption and thus in the maintenance of lipemic levels. The problem of fatty infiltration of the liver thus is not fully solved. (But see addendum.)

The liver is known for its detoxifying and inactivating powers of certain substances coming to it in the blood stream. The following serves as a recent example. Natural estrogens given by mouth are ineffective. The elegant proof as to the cause of this inactivation is as follows. If ovaries are transplanted intra-mesenterially so that their venous drainage enters the portal system they cease to have estrogenic effects, from which one infers the liver in some way renders the hormone inactive. M. J. Allen (1941) now brings forth evidence proving that the synthetic product, stilbestrol, which in every way has the same effects as natural estrogen is not inactivated while passing through the liver, and therefore may be given either per os or implanted as pellets intra-mesenterially or subcutaneously and still have its full effect. Just what happens to the natural estrogen while passing through the liver is another problem in liver physiology. (See also Selye, 1941; B. Zondek, *et al.*, 1941.)

This incomplete account of the multiple known functions of the liver may not be concluded without at least brief mention of what may be regarded as one of the most important of all, the hematopoietic function. Since the fundamental discoveries of Whipple and his associates and those of Minot, Murphy and Castle, investigations have been continued by numerous workers to unravel the mystery of the antipernicious anemia principle which is agreed on all sides to be elaborated, stored and

distributed by the liver. Jacobson and Subbarow (1941) discuss the possible chemical nature of this principle, judged from all knowledge gained thus far, and Formijne (1940) contributes experimental data on the nature of "the extrinsic factor" and "the reaction of Castle."

The work briefly reported by Crandall *et al.* (1941) doubtless will be of great importance 1, in rendering an experimental animal available (and which may be substituted for human patients) for the assay of liver extract for therapeutic use, and 2, by experimentation in clarifying "the etiology of the macrocytic anemias of man."

The vasculature and circulation of the liver. Earlier observations led to an estimate that about one-third of the blood of the liver was delivered by its artery. However from the observation of Grindlay *et al.* (1941) on the unanesthetized dog, the present author estimates that the ratio of hepatic arterial flow to portal vein flow may be more nearly one-seventh than one-third!

The oxygen tension in hepatic arterial blood is ca. 85 per cent; that in portal vein blood, ca. 50 per cent. The final outlet from the liver is the large hepatic vein, from two-thirds to six-sevenths of whose blood thus for the most part has passed through two capillary beds. The blood vessel walls are well supplied with nerve fibers. But the effective distribution of these nerves to the various vascular systems is in considerable doubt as to quantity and kind. Besides this the liver is richly supplied with lymphatics.

The veins of the liver of many vertebrates have a peculiar distribution of smooth muscle. In the hepatic veins and venules of the dog and amphibious mammals, the smooth muscle cells are not arranged in continuous sheets as in ordinary veins but grouped into slender spirally arranged bands and, especially where the hepatic venules empty into the hepatic vein, the band becomes much thickened and quite annular in disposition around the lumen, so as to provide a sphincter. Authors do not yet quite agree as to the structure of the vascular walls in the human liver but this much is certain, namely, that while the hepatic vein has much smooth muscle in circular and longitudinal sheets, the annular sphincters are also present at the vena caval ostia. These sphincters when closed, and at times they doubtless do close up the lumen completely, thus act not as the one-way membranous valves of ordinary veins, but as canal-locks or sluice-boxes which when closed reduce the rate of transport of fluid; they act thus in somewhat the same

way as the sphincters of the alimentary canal. (For discussion and literature on these structures see Tischendorf, 1939, and Pfuhl, 1932.)[3]

Recent studies have corroborated and extended this knowledge of the special sphincter and sluice-mechanisms. Block (1940) describes sphincter-like activity of the walls of frog's liver vessels evoked by the action of adrenalin and acetyl beta-methyl choline. Deysach (1941) working with livers of cats and rabbits, describes small endothelial tubes which are situated in the walls of the sublobular and central veins. The lumina of the latter communicate with those of the former by means of ostia which are guarded by sphincters. These ostia when dilated may permit the small endothelial tubes under certain conditions to be filled with blood. Upon closure of the sphincters large volumes of blood may be sequestered from the regular circulatory pathways of the liver and thus from the general circulation. Under other conditions the ostia may dilate again and the side chambers empty themselves, thus suddenly increasing rate of outflow from the hepatic vein. What the ratio of volume at maximum capacity of these chambers may be to that in the other hepatic venous pathways is difficult to determine but no doubt a method can be devised for an approximate estimation. In a histological study of turtle's liver Tyler (1941) showed that the distribution of smooth-muscle in the walls of portal and hepatic veins was much like that in the dog's liver, and the structures and arrangements of biliary ducts, arteries, parenchyma cells and lobules much like those in the human liver. The walls of the portal venules are practically devoid of all smooth muscle and the hepatic venules and capillary sinusoids have their smooth muscle cells arranged entirely in sphincter and spiral bands. The sphincters at the mouths of hepatic venules are thick, annular bands. (See plate 1 in Tyler, *loc cit.*) If the sphincters found in mammalian liver help us to explain the volume changes of the organ evoked by various agents (Bauer *et al.*, 1932; Deysach, 1941) these structures found in the turtle's liver should explain equally well, the volume changes exhibited by that organ under various conditions (Snyder, 1938).

Intrinsic vascular responses; their effects upon rates of metabolic exchanges. The presence of smooth muscle and the reactions evoked by autonomimetic drugs indicate an autonomic nervous supply to the sphincters. Anatomists have shown such a nervous supply to the

[3] L. B. Arey in Anat. Rec., 1941, **81**: 21, summarizes and discusses the intrahepatic musculature among mammals and illustrates the "throttling mechanism" with reproductions from wax reconstructions of them.

vasculature of the mammalian liver, although the finer details of the nerve-endings are still lacking (Pfuhl, 1932).

The fact that the liver responds to cholinergic agents suggested on the other hand that the hepatic outflow during vagal stimulation of the liver should contain "vagus-stuff." Experiments carried out on the turtle's liver proved this to be the case (Snyder, 1936). Since adrenergic agents when injected into the portal vein also evoke volume changes and flow rate differences it may be inferred likewise that during sympathetic nerve stimulation the hepatic outflow would contain a sympathin-like substance. Experiments by Cannon and Rosenblueth have shown this to be the case. (For literature see Rosenblueth, 1937.)

From the known general effects of these autonomimetic agents upon other organs and tissues, one would expect them to have antagonistic effects, but the conflicting reports in the literature have abundantly shown however that this is not easily demonstrated for the activities of the liver. The explanation for this conflict in the evidence is no doubt to be found in the fact that many of the experiments have been carried out with the organ *in situ* where it is under the influences of the manifold and variable activities of its fellow viscera, to which it is more than any organ highly sensitive. (See Bauer *et al.*, 1932; Katz and Rodbard, 1937; Grindlay *et al.*, 1941.)

Observations on the liver *in situ* are essential and important but, for an answer to the exact effects of autonomimetic agents or of autonomic nerve stimulation, especially upon the quantitative uptake or output of substances by the liver, experiments on the isolated surviving organ are more hopeful of reproducible results.

There is one source of error in both preparations, however, that has not received enough attention. In evaluating flow-rates and volume changes and probably also fate of substances, the exudates and lymph flow of the organ too often have not been observed and analyzed. Differences of observations among various works probably would largely disappear if changes in lymph and exudate flows were observed simultaneously with volume or flow-rate changes.

Figure 1, heretofore unpublished, is a reproduction of a smoked drum record, made during an experiment (2/1/1940). A continuously recording flow-meter was put in the inflow path; an automatic tilting vessel records rate of outflow. The upper trace line is a continuous record of the pH of the hepatic vein outflow; the second trace line records the lymph outflow in drops from a drainboard upon which the organ rests, the cut end of the lymph-vessels being open; the third trace-line records

the rate of outflow from the hepatic vein, each down stroke on the trace-line indicates the discharge of the tilting vessel of about 9 ml. capacity; the fourth trace-line records the time in ten-second intervals, and the fifth trace-line is a continuous record of the rate of inflow recorded by what is called a "rotameter." All the recording instruments have been carefully calibrated.

The changes in pH during the experiment vary from a high of 7.45 to a low of 7.39. The inflow recorder shows many spontaneous rhythmical oscillations, which represent varying resistances in the hepatic venous bed. At the arrow 30 gammas of acetyl beta-methyl choline

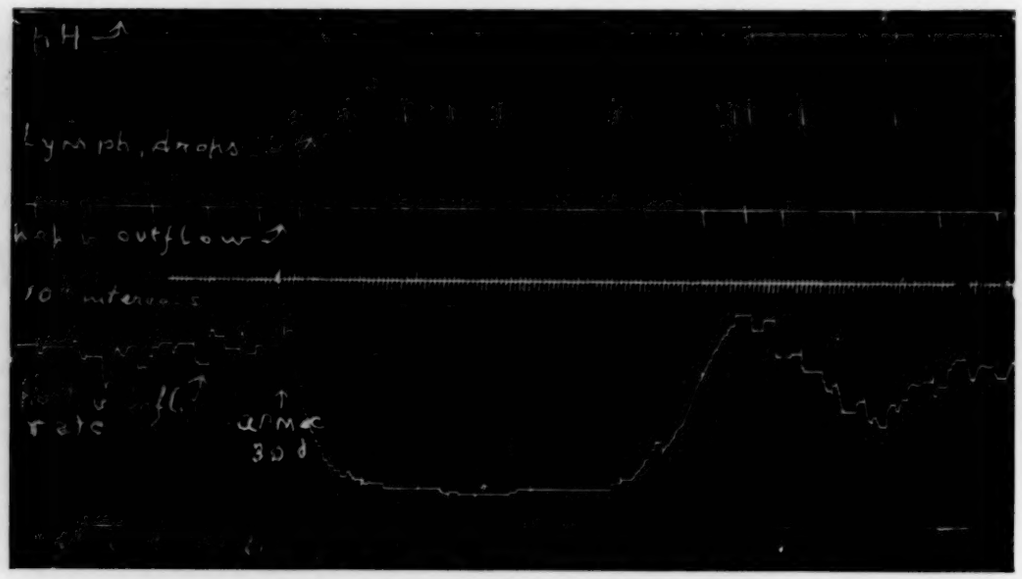

Fig. 1. Shows drum record of effect of 30 gammas of acetyl-Beta methyl choline on rate of inflow to and outflow from liver. See text for detailed description. Read left to right.

(ABMC) were injected into the portal vein. The effect of the agent comes on suddenly, causing at first a brief increase rate of inflow (dilatation of capillary sinusoids?) and at the same time a momentary increase in rate of outflow. This short period of increased outflow would be the result if the sphincters of the hepatic venules began to constrict in a peristaltic wave moving from their smaller branches out toward the heptic vein itself. Following this, the rates of both inflow and outflow decrease abruptly and profoundly; there is increase in the lymph outflow lasting until the rate of hepatic vein outflow begins to increase. Careful inspection of the records gives one the impression that the blockage to flow of fluid is in the hepatic venous system rather than in the portal

venous system. The head of inflow pressure having remained the same, the observed increase in transudate and lymph flow would be expected. The whole picture seems to indicate that the cholinergic drug, and therefore also motor vagal nerve impulses, stimulate the hepatic venous sphincters to constrict; this action erects barriers to the flow of fluid. The absence of smooth muscle in the turtle's portal venules and portal vein allows of no constriction or activity in those vessels; we assume they remain passive.

Figure 2 is a reproduction of a heretofore unpublished drum record showing the liver's response to 33 gammas of ABMC while in an oncom-

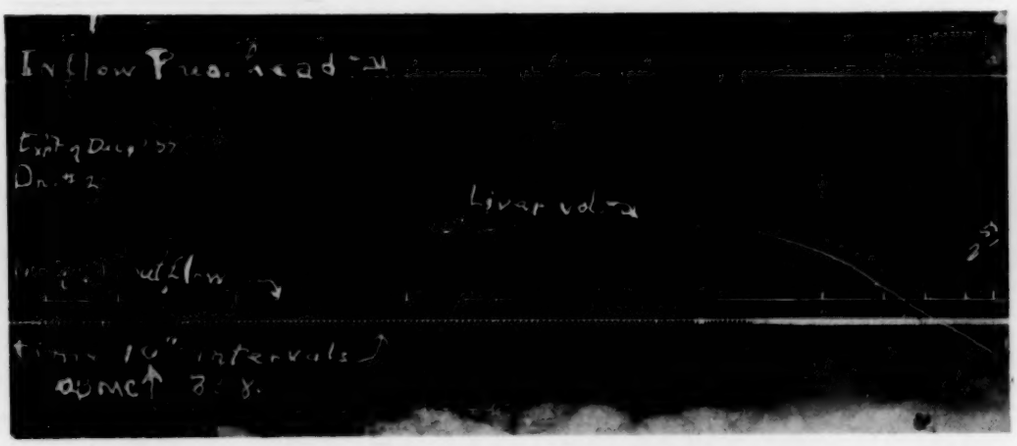

Fig. 2. Oncometer drum record, showing effect of cholinergic agent on liver volume; upward movement = decrease of volume. Time in 10 second intervals; drum greatly slowed down toward end of record. Signal = 33 gammas of acetyl-Beta methyl choline injected into portal vein. Third trace from bottom at left = tilting vessel recording hepatic vein outflow. Top line shows constant head of pressure at inflow. Read from left to right.

eter (Snyder, 1938). The outflow from the hepatic vein is recorded by tilting vessel. The upward movement of the plethysmograph recorder indicates decrease of liver volume. Exudate and lymph outflow, if any, entered the oncometer chamber and thus would have the same effect as increasing liver volume. The even course of the volume recorder before injecting the drug indicates that exudate was very small indeed and if it increased, during the drug effect, it prevented the recorder from exhibiting the full decrease of liver volume that the drug evoked.

The volume during the effect of epinephrin in similar experiments was apt to diminish, a prevailing increase in volume could often be

stopped by injection of this drug (Synder, 1938). "Epinephrin reversal" effects on flow through liver, when minimal effective doses were used, were observed by Snyder and Martin (1922). In these earlier experiments turtle livers were isolated and perfused at constant head of pressure (ca 12 cm. water column) from a set of reservoirs containing perfusing fluids of high and low pH levels and also with and without epinephrin. Concentration of the agent set at ca $1 \cdot 10^{-8}$ to 1 perfusate, and pH of ca 7.8 caused a decrease in rate of hepatic-vein outflow; but an increase of hepatic vein outflow, if the pH was ca 7.1.

If there are differences in synchronous inflow and outflow rates and especially if there are periods of profound changes in mean flow rate through an organ, the actual uptake and output of substances in the bloodstream by the organ cells must also vary greatly from time to time. To determine this proposition series of experiments such as described above were carried out, during which at intervals of 10 to 15 minutes samples of the inflow and outflow fluids were taken, analyzed and the data reduced to the standard terms of gram of substance gained or lost in the outflow per minute per 100 grams liver.

The substances thus determined were sugar, lactic acid, chloride, potassium, oxygen and carbon dioxide. The results were recalculated also in the same terms but without taking into account the synchronous differences between rates of inflow and outflow through the organ, that is on the old basis of differences in concentrations between inflow and outflow alone and on the assumption that the inflow rate always equalled the outflow rate. The results obtained by the two methods of calculation vary sometimes enormously as is shown in table 1, by Snyder and Tyler (1940b). Here the gains and losses in the liver output are compared with the input 1, in the case inflow and outflow rates are taken as equal, and 2, in the case that the actual differences between inflow and outflow rates are taken into the account. By the first method the glucose and lactic acid have gained in the output over the intake. By the second method both glucose and lactic acid at times are less, at times more. Put in terms of percent, the difference in values obtained by the two methods varies from 4 to 2800 per cent for glucose, from 5 to 228 per cent for lactic acid.

In view of their findings as to the fate of radio-activated lactate administered in rats, Conant *et al.* (1940) have suggested that it may be that lactate, in its apparent conversion to glycogen by the liver, may undergo a decarboxylation. A final answer to this suggestion may well be had by repeating the experiments on the isolated perfused organ under the conditions here recommended. If the decarboxylation

takes place in the liver, equivalent radioactivated CO_2 ought to appear in the outflow from the hepatic vein.

Following the method thus outlined, comparing actual input to output per unit time and unit weight of liver at room temperature, Snyder and Tyler (1940 a, b) have come to the following conclusions:

Oxygen consumption is at maximum when rate of perfusion of a Tyrode solution, saturated with oxygen, is at ca 20 ml. per minute per 100 grams wet weight of liver. Under these conditions ca 0.23 ml. oxygen is used up per minute per 100 grams liver. This oxygen consumption is greater than that of turtle-liver slices surviving in the Warburg apparatus, namely, ca 0.15 ml. per minute per 100 grams liver. The findings on perfused dog liver (Blalock and Mason, 1936), after being extrapolated for temperature differences, give a mean as great as 0.8 ml. per minute per 100 grams liver; for rat-liver slices the mean extrapolated figure, however, according to Minami's data is as low as for turtle liver, namely, 0.13 ml. per minute per 100 grams liver.

The rate of carbon dioxide production varies enormously on the other hand, the amount in the outflow sometimes being less than in the inflow. This suggests that carbon dioxide is being absorbed to form, possibly, ammonium-carbamate. The R.Q.s accordingly vary so greatly that they are meaningless. (See Addendum, last paragraph.)

There is nearly always an excess of glucose in the outflow over the inflow to the liver. If the pH of the perfusion fluid is high this excess of glucose output is greatly reduced and may become zero. If the content of the inflow in dextrose is high, and the perfusion rate high, then (according to Parnas and Baer, 1912) the glucose is absorbed by the liver and converted to glycogen. No glycogen determinations however were made. Lactic acid in the output by the liver exceeds the input whether lactic acid is present in the input up to 0.1 per cent or not. The absence of dextrose in the inflow increases the output of lactic acid from the liver. High pH of the inflowing perfusate reduced the excess of lactic acid in the outflow, so that at times there may be a deficit instead of an excess. Adrenergic agents here also markedly increase, and cholinergic agents decrease, the excess output of glucose and lactic acid from the liver over the input. The increase in glucose output, due to adrenalin, exceeds the increase in the mere perfusion rate. This suggests and supports the present generally accepted doctrine that adrenalin (and most probably sympathetic nerve stimulation) causes the liver cells to give up their carbohydrate stores directly. The decrease of glucose and lactic acid output produced by acetylcholine on the other hand so nearly parallels the decrease produced in perfusion rate

that we cannot be sure that acetylcholine (and by inference vagus nerve stimulation) directly inhibits the liver cells in their glycogenolysis. When the output of glucose from the liver undergoes a diminution it is a question as to whether its disappearance is due to a splitting into lactic acid on its way through the organ or to a conversion into glycogen. Our simultaneous determinations of both glucose and lactic acid gives evidence that the decreased output of glucose by the action of acetylcholine cannot be due to glucose splitting into lactic acid, for the lactic acid output at the same time is also decreased.

In order to detect if possible more precisely the *loci* of the effects of autononomimetic agents when injected in single, small doses into the turtle's portal vein, a series of experiments were carried out in which continuously recording flow-meters were introduced into *both* portal and hepatic veins. The observations and results permit the following interpretation (Snyder, 1941):

Since the portal vessels are devoid of smooth muscle they cannot be expected to respond to this class of agents. The observed responses to cholinergic agents, namely, shortlasting great increases in hepatic vein outflow accompanied by lesser- and longer-lasting decrease of inflow-rate must be due therefore to constriction of the hepatic vein and venules starting in a peristaltic wave at their sublobular origins and proceeding toward the caval orifice of the hepatic vein. This would account for the initial increase in outflow and also for a longer lasting resistance set up which in turn brings about the longer lasting decrease in inflow rate, and also the final effect on outflow, namely, almost complete obstruction, until the agent is destroyed.

The adrenergic effects observed are a slow persisting rise of outflow-rate and slow, persisting fall of inflow rate. To explain this it seems simplest to ascribe the increase in outflow to a sudden release of fluid from the parenchyma cells (which is accepted as one of the effects of adrenalin on the liver). This sudden increase in volume of fluid in the hepatic venules sets up a resistance to the inflow from the portal side, which lasts as long as the increase in the outflow rate. For the evidence and further discussion the reader should consult the original paper.

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ADDENDUM

Positive evidence of the efficacy of lipocaic in controlling fat-deposition in the liver will be found by Isabolinskaya, Bul. biol. et med. exper. U. R. S. S. **9:** 107, 1940, who finds the pancreatic extract to have the power "in most cases" of inhibiting the development of toxic fat-infiltration of liver. Gavin and McHenry, J. Biol. Chem., **141:** 619, 1941, now show that lipocaic has a differential effect on deposition of various fatty substances in the liver, preventing only that produced (in rats) when biotin is fed along with thiamine and certain other substances, whereas the "thyamine type" of fatty livers is prevented with choline and not with lipocaic.

Evans and Slotin, J. Biol. Chem., **141:** 439, 1941, in an elegant series of experiments, where they used radioactive C^{11} as a tracer, demonstrate that CO_2 is utilized by minced pigeon liver in the formation of alpha-ketoglutonic acid from pyruvic acid.

THE PRESENT STATUS OF THE SHOCK PROBLEM

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REVIEWS. The subject has been systematically reviewed in a number of texts and monographs (Blalock, 29; Cannon, 42; Harkins, 117; Y. Henderson, 121; Moon, 176; Rehn, 205; Scudder, 226; Turck, 246; Wiggers, 259); it has also been treated in symposia, editorials and numerous papers, more limited in scope (24, 33, 36, 43, 64, 73, 90, 98, 102, 109, 116, 120, 156, 164, 169, 170, 174, 175, 186, 190, 195, 200, 206, 210, 215, 245, 250, 265, 266). In view of these excellent surveys and sources of reference, another comprehensive, systematic, or historical review is neither needed nor intended. A review of existing reviews does leave the impression, however, that, if they have any shortcomings, these are a, that many writers have marshalled and oriented experimental discoveries so that they seem to support only one favored theory of shock; b, that, in the zeal to crystallize conceptions concerning the mechanism of shock, *conclusions* have been accepted too generously in place of *demonstrated facts*, and c, that the experimental conditions under which incontrovertible results have been obtained were not always carefully scrutinized and evaluated. Consequently, another survey of the shock problem will probably be of greatest use if it stresses some of these features. It is the author's intention, after a brief historical survey and orientation, to analyze the experimental conditions under which shock is best studied, to examine the validity of generally accepted conclusions in the light of present day knowledge, to reweigh the experimental support for disputed hypotheses, and, in a few instances, to reassign priority for ideas in accordance with experimental evidence therefor. Such an essay cannot favor any hypothesis; it will rather tend to emphasize discrepancies and gaps of information. Nor can it be expected to bridge these gaps by speculations or citation of opinions.

THE MARCH OF PROGRESS. The author's first review of the shock problem consisted of an essay written while he was a medical student in Ann Arbor. The report recalls the status of the problem in 1903. It emphasized 1, that most of the early hypotheses were originated in an

arm chair or at the desk, and that careful clinical observation and reflective thinking had failed to solve the problem; 2, that a change in thinking was in progress which transferred the fault from failure of the heart to failure of the peripheral circulation, and 3, that physiologists had apparently not yet become interested in a definitely functional disorder. At that time, indices of physiological text-books either did not list the word or, as in Schafer's well-known volumes, it read, "Shock—see Spinal Shock." The term *shock* had entirely different connotations for clinicians and physiologists.

The early hypotheses, ably reviewed by H. Fischer in 1870 (82) and by Groeningen in 1885 (110) seriously attempted to apply existing physiological knowledge to disease. This had many pitfalls and certainly did not prove adequate. In some instances, as in the frequently quoted papers of Malcolm (1893–1907) (160), it merely resulted in a curious confusion in applying known hemodynamic principles to the circulation.[1] When the hypotheses formulated by them agreed with those later supported by experimental investigation, this was purely fortuitous.

The experimental era began with the extensive investigations of Crile, published in his first monograph in 1890 (55). While his hypothesis resembled that propounded by Groeningen, it did have a background of experiments, many of which have become generally accepted. The experiments of Howell (136) constituted the next major attempt to elucidate the subject in the laboratory, and to this end he employed many procedures still used today. He concluded that shock may be either

[1] His earlier hemodynamic conclusions read, "Any treatment and condition tending to dilate the systemic vessels by diverting the flow of blood from the internal to the superficial parts must tend to increase the blood pressure in the carotid, by causing its contraction . . ." (1905).

Later, in attacking Crile's hypothesis which involved arteriolar dilatation the issue was confused with passive changes in larger arteries. "When a series of vessels in the normal human body is contracted the blood pressure in the affected area is lowered, whilst the flow becomes more free and the pressure rises in some other part or parts of the vascular system." . . . "Again when small arteries contract the volume and pressure of blood within them are reduced and the lumen may even be occluded so that blood pressure is completely removed" (1907). . . . "Thus, in the large and small vessels and practically in all conditions a lowering of blood pressure in any particular artery or vascular area is accompanied by contraction and not a relaxation of the vessels concerned" (1907). Again, "In conclusion I would urge that as the state of shock develops, there arises an intense and increasing stimulus to contraction of the vascular system, which in advanced cases may give rise to a low blood pressure from overaction of the heart" (1910) (!).

of cardiac or vascular origin. He also made the significant observation "that operations which were sufficient to produce shock in one animal might in another have little or no effect of this kind." The efforts to devise a standard procedure that unfailingly produces shock seems as hopeless today as in 1903.

Once an interest had been created, physiologists were not slow to test various hypotheses. The experiments of Porter (1907–08) (202), of Seelig and Lyon (1910) (225), made untenable the concept that exhaustion of the vasomotor center initiates shock. Y. Henderson (1908) (122) stressed decrease in venous return and cardiac output as initial factors and developed his acapnia theory. Meltzer (1908) (172), with an experimental background of observations on intestinal motility, suggested a broader conception of shock which stressed dominance of the inhibitory side of all reflex actions.

During the years of the First World War (1914–18), the curve of interest among physiologists rose sharply with the result that they were not only actively at work in various laboratories in the United States and England but that teams composed of physiologists and surgeons cooperated in the war zones of France to utilize the extraordinary opportunities for studying shock in man. (For reviews see Cannon, 42; Harkins, 117.) These observations produced new problems for reinterpretation in the calm of the experimental laboratory. Such shuttling of problems between the field and laboratories of basic science proved of immense value, and when the smoke of battle had cleared away the following definite advances could be recorded: 1. It seemed highly improbable that shock was due either to *a*, exhaustion of the vasomotor center; *b*, to adrenal-medullary deficiency; *c*, to acidosis; *d*, to acapnia, or *e*, to fat embolism. 2. It seemed quite probable that, in various catastrophies, a toxic factor (histamine) combined with loss of plasma or blood caused a reduction in circulatory volume which impaired the filling of the heart and its output, and that this was the cause of the progressive lowering of arterial pressure and eventual death through asphyxia. (For reviews of that period see Cannon, 42, and Wiggers, 259.) Moreover, following a suggestion of Gesell (96), investigators endeavored to distinguish between initiating and sustaining factors, and many of them began to realize that the initiating agent might not prove the sole cause of death, if indeed it be involved at all.

As far as physiologists were concerned, the years 1923 to 1941 were noteworthy chiefly in an awakening of interest in the possible relation of the adrenal cortex to shock and in the efficacy of cortical preparations in

its treatment (237, 238, 239, 240, 241, 229, 230). The probability that histamine represents the guilty toxic agent seemed to receive less and less experimental support. The possibility that potassium may represent a common toxic depressant agent was extensively investigated by Zwemer and Scudder (226, 269). Aside from occasional contributions, chiefly of a confirmatory nature, the mechanisms of shock received scant attention in physiological laboratories. On the other hand, the era was characterized by an acute awakening of interest among experimental surgeons, among whom the teams led by Blalock, L. Dragstedt, Freeman, Lenhart, O'Shaughnessy, Phemister, Slome, etc., may be mentioned. The subject was also investigated systematically from the viewpoint of the pathologist through the leadership of Moon. The ways in which these several lines of approach modified our concepts of shock can be gathered best from a perusal of the recent monographs by Blalock, Moon and Scudder. Finally, and most important, it represented a period in which the knowledge gained was applied in a practical way by surgeons. However, as Harkins (117) states in an admirable recent review, "the question of shock is not yet settled, and, while transfusion therapy is helpful, it is not the entire solution of the problem."

DEFINITION.[2] As Meek has recently said, "every worker has given a definition of shock to illustrate his own conception of the condition, and this is, of course, what definitions are good for." In this spirit, a definition is again suggested which expresses the extent to which we ought to commit ourselves on the basis of a critical examination of available clinical and experimental evidence. *Shock is a syndrome resulting from depression of many functions, but in which reduction of the effective circulating volume and blood pressure are of basic importance, and in which impairment of the circulation steadily progresses until it eventuates in a state of irreversible circulatory failure.* Such a definition recognizes the involvement of systems other than the circulatory and acknowledges the detrimental effects that such derangements have on the organism as a whole. It also stipulates that the neuromuscular, glandular and visceral phenomena may not all be secondary to circulatory changes. At the same time it concedes that progressive failure of the circulation is of basic importance from etiologic, prognostic, and therapeutic standpoints. Following precedent, we shall limit our discussions of shock to its circulatory aspects.

EXPERIMENTAL SHOCK. The conditions under which experiments are performed frequently determine the results and their applicability to a

[2] For a concise list of definitions see Harkins (117).

broad problem. This is certainly true in the study of shock and allied conditions, and may be one of the reasons for the differing results that continue to be reported. Under the circumstances, the author will be permitted—and perhaps expected—to discuss certain problems of experimentation, concerning which he has formed strong convictions during more than 30 years of active participation in research on the circulation.

The problem of anesthesia. It is frequently claimed that the reactions of shock can only be studied in unanesthetized animals. Although useful for the study of neuromuscular and visceral reactions and of changes in the volume and composition of the blood, experience has shown that—the problems of infliction of pain and utilization of dynamic apparatus quite aside—the cardiovascular responses may be even more complicated and difficult to interpret in unanesthetized than in properly anesthetized dogs. The dog is an animal which responds with tremendous variations in heart rate and blood pressure to trivial auditory, visual and surface stimuli, as well as to psychic influences. The latter may be minimized by training, but, despite claims to the contrary, cannot be eliminated entirely for studies of cardiovascular problems. The best criterion of normality in trained dogs is the persistence of their natural phasic sinus arrhythmia. However, during the course of a fairly rapid hemorrhage, which can be created painlessly under initial basal circumstances, intense psychic stimulation, manifested by movements or even struggle, seems to be caused by the cerebral anemia. The tremendous increase in respiratory rate and depth, exceeding in degree anything encountered in man, creates such an interference with the dynamics of the circulation that conclusions of consequence can rarely be drawn. While decerebration has its uses in cats, it probably causes even greater disturbances of the circulation than anesthesia, in dogs.

Since anesthesia is unavoidable in many types of experiments, and it is indeed questionable whether its elimination is desirable in shock experiments, it is important to utilize a type which interferes least with natural cardiovascular and nervous reactions. It is also necessary to comprehend the directions in which the anesthetic may be expected to modify responses. Volatile anesthetics cannot be administered so as to maintain an even concentration in the air passages and blood and, therefore, invoke many actions which confuse the reactions of shock. The pressure pulses, particularly, show variations that are not recognized in electrocardiograms or mean arterial pressure tracings.

The ideal anesthesia is one given intravenously, which produces the

least deviation of natural reflexes and cardiac actions, which maintains an even anesthesia for hours without readministration and which, of course, does not induce circulatory states that can be confused with shock.

Among the many anesthetics, we no longer consider chloretone a suitable anesthetic for dogs. Chloralozane is satisfactory and particularly useful in experiments in which a slow heart and somewhat exaggerated vascular reflexes are an advantage. However, after numerous trials of many anesthetics during the past 12 years, our laboratory regards *morphine-barbiturate* anesthesia perfectly satisfactory for cardiodynamic studies, including shock and hemorrhage. The particular barbiturate used is chiefly determined by the duration of anesthesia required. For prolonged experiments, we prefer sodium barbital, since readministration is not required.

In view of the fact that certain experimenters believe that barbiturates cause significant depression of the heart, circulation and nervous reflexes, and some, indeed, claim that barbital *per se* causes shock (4), it is necessary to defend its choice as an anesthetic.

As emphasized by Tatum (242), the reactions of dogs to barbital depend not only on the dosage but on the rate of its administration. Furthermore, it is not sufficiently emphasized that many of the undesirable effects of barbital are eliminated when it is preceded by morphine. The routine practice in our laboratory is as follows: A preliminary subcutaneous injection of morphine sulfate (ca. 3 mgm./kilo) is given a half hour previously. About two-thirds of a calculated anesthetic dose (175 mgm./kilo) is injected into a small leg vein over a period of 5 minutes. The effects upon reflexes, state of relaxation, respiration, etc., are noted. Cerebral excitement or intensification of respiration is uncommon. As much of the remainder of the calculated dose is then administered, even more slowly, until the animal just fails to respond to cutaneous stimuli; but the tendon reflexes are exaggerated and the corneal reflex is retained. In other words, *the anesthetic dose is determined by biological standardization for each animal.*

In a dog thus anesthetized, respiratory movements are slightly depressed, an advantage in that normal CO_2 tensions are maintained in the alveoli and blood and the excessive breathing of unanesthetized dogs does not obscure dynamic changes of the circulation. Although barbiturates and morphine both depress gastro-intestinal movements and tonus, intestinal contractions do occur, and viscero-somatic as well as somato-visceral reflexes remain active (191). Bouchaert and Hey-

mans (34), among others, claim that barbital suppresses sinus and aortic pressor responses. This we cannot confirm; moreover, Heymans' first observations on carotid sinus reflexes were made partly in our laboratory (128) upon dogs anesthetized with barbital. Stimulation of pressor fibers (central vagus and sciatic nerves) are capable of yielding extraordinary increases in mean pressure. We frequently obtain elevations of mean pressures to 200–250 mm. Hg by stimulating the central ends of both vagus nerves. Normal blood pressure levels are maintained for 12–24 hours when no experiments are carried out and the dog's temperature and water-balance are maintained. Indeed, such dogs recover completely and, subsequently, display no abnormality of action or behavior.

On the other hand, it cannot be claimed that barbital is without effect on the cardiovascular system or the reactions that may occur in the unanesthetized state. Barbital does tend to increase heart rate through diminution of vagal tone (111). However, extreme doses (ca. 500–1100 mgm.) are required to abolish such tone completely. Given with morphine, a natural sinus arrhythmia often persists, but even when this does not occur, section of the vagus nerves or atropine causes an additional increase in heart rate. Nor are peripheral vagus pathways blocked; stimulation of the peripheral end causes slowing or standstill of the heart and, in the case of the left vagus, leads to various types of A-V block. These are yearly classroom demonstrations in our school. In fact, the greatest cardiac acceleration which follows use of morphine and barbital is never more than that which occurs when a quietly resting dog is aroused. Shock induced in such barbitalized dogs merely resembles that of persons whose heart rate and vascular system have been altered before a catastrophe by psychic stimulation, e.g., fear, anxiety, excitement, fright, etc. Nevertheless, experimenters must recognize that the early increase in heart rate and progressive acceleration are less than under natural conditions and may even be missed in barbitalized dogs. For their evaluation, chloralozane anesthesia is superior.

Despite the increase in heart rate occasioned by barbital, arterial pressures quickly readjust themselves at approximately normal levels. Since barbital has been observed to dilate visible vessels and those of perfused organs, this is generally attributed to compensatory vasodilatation. It is difficult to prove, however, that this is the chief, or even an important mechanism. To us, it seems more probable that the enlarging spleen (1, 2, 51, 108, 115, 227) stores blood, reduces the venous return and keeps the minute output of the heart practically constant, despite

the increase in heart rate. Creation of such a greater reservoir may constitute an arrangement by which reduced blood volumes during shock and hemorrhage are better compensated through splenic contraction. Amytal also causes some hemodilution (1, 2, 74). Through these alterations, barbiturates should exert a protective rather than a deleterious influence in the production of shock. Seevers and Tatum (228) reported some congestion of viscera, and especially of the brain, after use of barbital; but it must be stressed that this occurred after chronic barbiturate poisoning and not after a single anesthetic dose. Moreover, death was not due to shock, but generally to convulsions.

Equivalence of experimental conditions. In experimental studies of shock it has seemed important to duplicate in anesthetized animals, as far as feasible, catastrophies that occur in man. The procedures employed in accordance with this aim include hemorrhage, crushing of muscles, bones and testes, infliction of burns, production of intestinal obstruction, exposure and manipulation of intestines, radiation of the abdomen, introduction of foreign material into the abdominal cavity, etc. It has been learned that all of these can cause shock, but that they do not invariably do so. Why this is true we do not know; some suggestions will be considered later. But when shock does eventuate as a result of identical procedures, different groups of investigators report different reactions. In order to evaluate to what extent this is due to the animal's resistance or susceptibility, the conduct of experiments must be scrutinized. It is important that all discoverable experimental variables be eliminated, or that their influence be assessed. Some of these may seemingly be of little importance but actually are determinants of variable results. For example, the changes of an animal's temperature may have a greater importance in the development of shock than has been commonly recognized. Fundamental studies (100, 208) seem to indicate that cutaneous blood can be mobilized to compensate for reduced blood volume only when the skin is kept moderately warm; the reactions of cooled and overheated animals differ markedly in physiological tests. While it is difficult to obtain conclusive evidence, Blalock[3] recently recorded his impressions that shock may be produced more readily if animals are kept warm than if they are allowed to cool. It is a coincidence that Werle and I (266) recently formed similar impressions.

In the hope that use of more drastic measures may cause experimental shock with greater certainty, other experimental procedures have been

[3] Address before the American Heart Association, Cleveland, June, 1941.

tried, such as prolonged hyperthermia or freezing, placement of ice-water in the abdominal cavity, rectum or intestinal loops, cauterization or traumatization of the intestines or liver, vigorous massage of the stomach, etc. Such experimentation may yield useful information, but the results must be applied to the broad problem of shock with reserve and caution.

Our duty as experimentalists is not concluded by producing shock and studying, as far as methods allow, the circulatory changes that take place. We must modify experiments cleverly in order to test the validity or unsoundness of numerous clues. In so doing, nerves must be cut and stimulated, important arteries or veins need to be sacrificed for insertion of proper cannulae, flowmeters or pressure recorders, etc. The plan of experimentation may even require opening of the chest or abdomen, manipulation of viscera, placement of oncometers, etc. All of these acts themselves modify the delicate balance of the circulation and its labile reflex control far more than the recording mercury manometer reveals.

Artificial respiration, opening of the thorax and exposure of the heart are required only in particular types of cardiodynamic experiments on shock. In the use of artificial ventilation, acapnia and chemical changes in the blood are largely avoided if artificial respiration is reduced to the point at which mild natural breathing just continues. Presence of Hering-Breuer reflexes, indicated by contraction of the diaphragm with each deflation of the lungs, is also a good criterion of a well adjusted artificial respiration. The degree to which pulmonary blood flow is impaired by the positive intrapulmonary pressures can easily be checked, from time to time, by noting the extent to which arterial pressure rises during momentary discontinuance of artificial respiration. The change should not be great. If low artificial respiration fails to maintain adequate oxygenation, as indicated by the darkening of arterial blood or attempts of the animal at deep spontaneous breathing, it is better to mix a little oxygen with respired air, than to increase the rate and depth of lung ventilation. I always feel that young investigators in the process of training have made considerable progress when they have mastered the art of inducing anesthesia and of giving artificial respiration properly. Many experimenters unfortunately have never learned this, or do not choose to give attention to it.

Opening of the chest, despite the avoidance of significant hemorrhage and of cutting numerous intercostal nerves, causes immediate changes in the pressure pulses which cannot be differentiated from the initial stages of hemorrhage or of shock due to trauma. The reasons remain

unsolved and deserve further study. These deleterious effects can be neutralized by maintaining a continuous slow infusion of warm saline and by slight compression of the thoracic aorta above the diaphragm, i.e., by use of the "controlled circulation preparation" (Wiggers, 260). These expedients which have proved so useful for experiments limited to cardiodynamic problems are not permissible in studies of the shock problem owing to the hemodilution incurred. Unless other expedients can be found which restore normal cardiodynamic conditions in open chest experiments, it must be recognized that we are starting with hemodynamic changes that have all the earmarks of the incipient stages of shock. However, there is one difference. If the anesthesia, artificial respiration, and temperature of the animal are properly maintained, the condition does not generally progress as in traumatic shock; on the contrary, it may improve after several hours. Consequently, significant information can still be gained regarding the changes produced by superimposed insults.

The proper evaluation of an animal's circulatory condition prior to use of shock-producing agencies cannot be over-emphasized. Since the qualitative and quantitative characteristics of *central arterial pressure pulses* are of the greatest service in forming such judgments, it is regrettable that their optical registration has been so slow in superseding recordings of mean arterial pressure.

In testing the mechanisms concerned in the initiation and progression of shock, it has often proved necessary to adopt methods for causing circulatory failure that bear no resemblance to those employed by Nature. The purpose of such experiments has frequently been misunderstood, with the result that experimenters have been criticized, and have criticized each other, as to the unapplicability of results so obtained. The category of procedures to which we refer includes prolonged strong stimulation of afferent nerves, injections of epinephrine, fat emulsions, muscle and tissue extracts, blood and serum from dogs in shock, administration of peptone, histamine, potassium and other agents; complete obstruction and subsequent release of blood flow from certain territories; also compression of the vena cava or aorta, pericardial effusions, occlusion of pulmonary vessels, reduction of plasma volume by plasmapheresis, prolonged intensive diuresis, etc.

In interpreting the factors responsible for shock, it is important that the fundamental purpose of such experiments be kept in mind. Most of these procedures may not have reduplicated the phenomena of shock produced in man, but they have proved useful in giving or testing clues

as to the nature of the disorder (see recent discussion by author, 266). However, it is equally obvious that the sequence of changes found in such clever experiments cannot be transferred directly to shock produced by more natural methods.

CRITERIA OF SHOCK. In order to study shock, criteria are necessary to determine when it exists. In such decision, the experimenter who works with anesthetized animals is deprived of many signs and symptoms that aid in its clinical diagnosis, e.g., changes in facial expression, motor and sensory depression, the appearance of the skin, sweating, etc. However, it is questionable whether shock, in the commonly accepted usage of the term, can be differentiated even clinically from pseudo-shock *in its incipient stage*. Blood pressure changes are generally admitted to be unreliable during the early stages; pressures may be normal or even high while forces which initiate shock are operating; or, they may be low, as a result of conditions not considered to be shock. The changes in heart rate are without value both in animals or man (144). Even the characteristic form of arterial pressure pulses and changes in venous pressure *during early stages of shock* are reduplicated by many other conditions.

During the progressive stage, the evidences become clearer. The best criterion is the coexistence of a *progressive* decline in central venous pressures, in cardiac output, and in arterial pressures. The first two are difficult to measure routinely, but in animal experiments qualitative and quantitative changes in the central arterial pressure pulses permit judgment as to changes in cardiac output and the fullness of the arterial system. With the introduction of optical manometers applicable to selected surgical cases, the direct registration of pressure pulses should prove increasingly more valuable. Preliminary studies by Volpitto, Woodbury and Hamilton (247) clearly indicate that the changes which occur during progressive stages of shock in man resemble those found in experimental animals. Lacking such facilities, the *progressive* fall in arterial pressures and the decrease in pulse pressure remain the most satisfactory general criterion during the progressive stage of shock.[4]

According to some investigators (for reference see Moon, 176; Scudder, 226), other signs, such as demonstrable reduction in blood volume and hemoconcentration, may even precede the decline in venous and arterial

[4] It should scarcely require re-emphasis that pulse pressure of experimental animals cannot be measured by the recording mercury manometer. Unfortunately, this elementary fact is still not appreciated by many otherwise able investigators.

pressures. According to others (for references see Blalock, 29 and Harkins, 117), hemodilution sometimes persists when irreversible stages have been reached. This, at least, is true; certainly not every human subject with hemoconcentration or reduction in blood volume develops shock. Dominated by current emphasis on the importance of blood studies, erroneous diagnoses of clinical and experimental shock are unquestionably being made on the basis of hemoconcentration. Beneficial effects are claimed for various forms of therapy in instances in which it was never shown that the subjects were in a state of shock which would have proved fatal without treatment. Hemoconcentration is a valuable sign, only when it occurs in conjunction with the dynamic criteria mentioned above.

Since one of the outstanding characteristics of shock is its fatal tendency, shock, in a highly restricted sense, can perhaps not be said to exist until a stage of irreversible circulatory failure has developed. We have substantiated observations of others that blood pressures may be kept at very low levels (50–60 mm. Hg) and cardiac output may remain materially reduced for 2–3 hours by bleeding, yet recovery occurs in some animals when blood is restored to the circulation. Have such animals been rescued from shock, or did a state of shock never exist? We incline to the latter view. It is apparently possible to have all the signs without a state of shock.

Investigators frequently stress the advent of death as evidence that shock has been produced. However, such an accident, without critical relation to the previous course of events, may be without value. Sudden death through respiratory failure is an occasional accident in anesthetized animals during any state of hypotension and must not be confused with death due to shock. Such respiratory failure may be due to a neurogenic factor. Thus Mann (163) found that deep anesthesia may abolish all respiratory reflexes except inhibitory ones so that stimulation of an afferent nerve such as the vagus causes a permanent apnea which is followed by a rapid decline in blood pressure and cardiac failure. We have had similar experiences in deeply anesthetized animals subjected to critical hemorrhages, but always found it possible to revive them by prompt use of artificial respiration and small transfusions.

Autopsy findings. Within recent years, evidence has been accumulating that shock due to various causes shows distinctive changes at autopsy. According to Moon, "marked diffuse congestion of capillaries and venules in visceral areas, especially in the lungs, liver, kidneys and serous and mucous surfaces; edema, effusions into serous cavities and

capillary hemorrhages," are present in all forms of shock except hemorrhage, in which pallor and dryness occur. Curiously, the vessels of somatic structures do not appear to be affected.

However, differences of opinion still exist with regard to the uniformity with which such pathological changes develop in unquestionable death from shock.

The following tabulation gives a partial list of the variations presented in representative pathological reports:

Blalock (27) Brooks and Blalock (37)	Capillary congestion, small hemorrhages, early necrosis in small intestines after hemorrhage.
Cornioley and Kotzareff (quoted by Moon)	Hemorrhages into stomach, liver, lungs, heart, pericardium, etc., after traumatic shock, in rabbits.
Davis (60) Davis et al. (61)	No splanchnic congestion after hemorrhage or traumatic shock—pulmonary edema, cardiac dilatation, liver necrosis after adrenalin shock—splanchnic congestion, etc., after histamine.
Erlanger and Gasser (76)	No ascites—marked congestion and hemorrhages of intestinal mucosa—increased blood-tinged intestinal secretions—liver not congested—all, in various types of shock studied.
Freeman et al. (93)	Congestion and edema of viscera after hemorrhage.
Klemperer et al. (146)	Focal or fused hemorrhagic lesions in stomach and gut after epinephrine.
Mann (162)	Primary dilatation of splanchnic vessels; later, congestion, following intestinal manipulation.
O'Shaughnessy and Slome (190)	Pallor of abdominal viscera and omentum after traumatic shock—congestion and edema after histamine.
Simonart (230a)	General dilatation of capillaries and plasma, transudation after burns and histamine—none in traumatic shock.
Keeley et al. (143)	Ischemia of intestines, no hemorrhages—lungs dry and slightly congested, spleen and liver firm after thermal trauma.
Turck (246)	Purplish discoloration of gut and venous congestion of abdominal viscera, in toxemic shock.

Wallace, Fraser and Drummond (248)	Report that surgeons performing abdominal operations in cases of wound shock noted only pallor of intestines—venous congestion never observed.
Whipple et al. (252)	Congestion of gastro-intestinal tract, liver, kidneys and lungs—engorgement and swelling of mucosa after toxemic shock.
Zwemer and Scudder (269)	Engorgement of intestines, lungs, etc., after trauma. Bloody peritoneal fluid, subserosal ecchymoses, swollen kidneys, petechial hemorrhages in lungs after intestinal manipulation.

The spleen has been reported both as large and congested (76, 122, 252, 269) and as firm, contracted, anemic and dry (143, 157, 176, 177 223).

While the pathological changes found at autopsy should be more carefully noted by experimenters, it does not seem that the picture is sufficiently constant to permit verification of a diagnosis of shock by post-mortem studies.

THE REDUCED VENOUS RETURN AND DECREASED CARDIAC OUTPUT. Reduction in the volume of blood returned to the heart is the keystone of all modern conceptions of shock. Actually the idea is a very old one. It dates from the classical experiments of Goltz (1864) (103) who demonstrated that sharp taps on the abdomen of a frog caused the heart to stop and that, upon resumption of its beat, little blood was expelled, because it had accumulated in the abdominal vessels and could apparently not be driven back to the heart. It was supported by observations attributed to Salathé (220) that acute circulatory failure can be produced in rabbits by suddenly tilting them from a horizontal to a vertical position. This is fundamentally similar to the "gravity shock" which occurs in certain individuals on standing. (For review of recent work, see V. E. Hall, 113.)

Splanchnic congestion was included in descriptions of shock-like states by Groeningen (110), Fischer (82), Crile (55), and Romberg and Pässler (213). All sensed correctly that the consequent reduction in cardiac output is the cause of the small, thready pulse. *However*, all attributed the decline of arterial pressure to diminished resistance in the splanchnic arterioles. That reduced venous return and decreased cardiac output are likewise responsible for the decline of arterial pressure was first suggested and largely developed by Y. Henderson (122, 123, 124, 125).

This important contribution of Y. Henderson to the analysis of

the dynamics of shock is generally overlooked in reviews on shock,—credit for the *idea* being sometimes given to subsequent investigators. This is in part due to his concurrent emphasis of acapnia as the factor responsible for respiratory failure, tachycardia, increased cardiac tonus, as well as failure of venous return in circulatory failure. With abandonment of the acapnia hypothesis, this clear and fundamental analysis of the cardiodynamics of shock should be given the credit it deserves. As early as 1908 (122), Henderson showed clearly that reduction of venous return reduced the stroke volume and how it did so (see Ref. 122, Fig. 1, p. 146). He further showed that excessive pulmonary ventilation decreased the diastolic filling and systolic discharge of the ventricles and, since both could be increased temporarily by saline infusion, the proper inference followed that reduced filling resulted in decreased output and fall in blood pressure. A fair evaluation of Y. Henderson's numerous contributions indicate a keen insight into the dynamics of the circulation responsible for the low pressures of shock. However, a careful scrutiny of *all* his published work fails to reveal experimental data which prove that such a cardiac mechanism operates in experimental shock due to trauma, intestinal manipulation or the other numerous ways in which shock has been produced. The credit for producing actual evidence that cardiac output—estimated by gasometric methods—does decrease in experimental shock produced in many different ways would seem to belong to Blalock and his associates (26, 140).

It is true that there have been—and still continue to appear—reports purporting to demonstrate reduction in venous return by observations on venous pressures. Clinicians always stressed the collapsed or invisible veins of the skin and the feeble jugular pulsations. However, decreased venous pressures cannot be judged from the appearance of surface veins (cf. Eyster, 78). Many experimenters (39, 55, 161, 178, 225) have reported decreased peripheral venous pressures in shock. However, Penfield (193) observed an increase, while Erlanger, Gesell and Gasser (77), and Bellis and Wangensteen (23) report only insignificant changes in jugular and inferior caval pressures, respectively. We must insist on clearer thinking with respect to the significance of venous pressure measurements. The pressure as measured in peripheral veins is no more an index of right auricular pressure than a blood sample from a peripheral vein is a criterion of mixed venous blood. That venous pressures measured elsewhere than in or near the right auricle are useless in estimating changes in venous return during shock is particularly clear

as a result of observations of Blalock and his associates (30, 32) that the reduction of flow from various regions is by no means equal during profound shock or hemorrhage. Furthermore, as Henderson and Barringer (123) pointed out, ventricular filling in the closed chest is not determined by the actual pressure in the central veins but by the difference between intra-auricular and intrathoracic pressure, i.e., by the "*effective venous pressure*" (cf. also Wiggers, 256). Since the tonus of respiratory muscles, upon which the magnitude of negative intrathoracic pressure depends, may conceivably alter in shock, it is of great importance to measure *effective right auricular* rather than actual central venous pressure.

In accordance with such reasoning, the writer in 1918 (257) believed he had made a significant contribution in showing that effective venous pressure, measured differentially, falls after infliction of trauma and intestinal exposure. I am now worried lest the original venous pressures may have been elevated by use of ether. Further, such observations do not permit one to estimate to the extent to which such a decrease is due to changes in intrathoracic or venous pressures. It is certainly more informative to record intrathoracic and central venous pressures separately. Such observations during the progress of shock are still needed in order to complete our picture of the dynamic phenomena. In addition, it must be kept in mind that while central venous pressures ordinarily reflect changes in volume of returning blood, such pressures are determined by the balance between rate of return flow, the size of veins and the rate with which blood is pumped away by the right heart. (For recent observations cf. Holt, 131.)

Finally, the majority of investigators, in efforts to fit experimental facts together, have assumed that venous return and cardiac output are necessarily decreased in proportion to a measured reduction in total blood volume. This is certainly not true in early stages of hemorrhage, for Meek and Eyster (171) showed that hemorrhage equal to 2.1 per cent of the body weight, or 28 per cent of the estimated blood volume, may not decrease cardiac output at all, presumably because reserve blood from the spleen, liver, skin and, perhaps, the lungs is placed in active circulation. Unquestionably, similar compensatory reactions occur during shock. *We may conclude*: Our current view that reduced venous return and decreased effective venous pressures are significant factors in the initiation and early progression of the circulatory failure in shock is strongly suggested by experimental and clinical observations; but it could be supported by more crucial experiments. Whether the

progressive decrease in venous pressures is the ultimate cause of irreversible circulatory failure or whether other precipitating factors enter, has not yet been demonstrated experimentally (cf. page 109).

THE INITIATING AND CONSEQUENTIAL MECHANISMS OF SHOCK. A satisfactory explanation of the initial reduction of the venous return would go a long way in establishing the cause of shock. Two fundamental ideas dominate the current literature, viz., 1, that the circulating volume is reduced by hemorrhage or local loss of plasma, and 2, that blood stagnates in capillaries and is thus removed from effective circulation. These conceptions are not mutually exclusive; in many instances the chief arguments revolve about the question which is cause and which, effect.

As Harkins (117) has properly emphasized, an initiating factor is the cause of shock, in the same sense that the diphtheria bacillus is the cause of diphtheria. However, in both cases, the progress of the disorder and the death that frequently occurs are consequences of such a cause. Indeed, death may be prevented, even when a causative agent persists, if the secondary consequences can be avoided or treated. Hence, the consequential effects which lead to irreversible circulatory failure are equally as important as the initial cause of shock. Unfortunately, it is not easy to separate causes and effects in various forms of shock; the factor which is a cause under one condition may prove to be an effect under other circumstances. It is becoming increasingly obvious that attempts to attribute shock to a common initiating factor, must probably be abandoned.

It cannot be disputed that significant decrease in blood volume is an important primary factor in hemorrhage and in the severe dehydration that follows protracted vomiting, prolonged diarrhea, excessive loss of gastro-intestinal secretions or their loss by drainage, loss of serum from wounds and burns, formation of large inflammatory exudates, etc. Blalock (29) and Harkins (117) have recently reviewed the overwhelming evidence that local loss of fluid at the site of trauma or from extensive burns is the important factor in the initial reduction of cardiac output. Such loss of fluid, if rapid and great, may, as in large hemorrhages, prove fatal due to respiratory failure. It can be postulated, that when the circulation is barely maintained for hours with the aid of compensatory mechanisms, this leads more gradually to general asphyxiation. Capillary stasis and increase in capillary permeability could be one of the consequences. The increase in capillary capacity reduces the effective circulating volume, and loss of plasma decreases the actual blood volume

further. A vicious cycle is obviously established. It is apparent that, according to this view, capillary stasis and generalized loss of plasma are consequences, not an initial cause, of shock.

However, an initial loss of fluid, sufficient to affect venous return significantly, is not apparent in many infectious or toxemic conditions which lead to shock. Moreover, since evidence can also be cited that toxic agents are absorbed when tissues are injured, and that nervous reflexes may affect the peripheral circulation, the view developed that, in such cases, changes in capillary capacity and permeability constitute the primary factor, and that changes in blood volume are secondary.

FACTORS RESPONSIBLE FOR CAPILLARY STASIS AND INCREASED PERMEABILITY. Since changes in capillary capacity and permeability occur either as primary or secondary phenomena in many instances of shock we shall advance our analysis of the peripheral circulatory failure by examining systematically the mechanisms by which such changes could be brought about.

Primary arteriolar dilatation. The arterioles are the terminal stopcocks of the arterial tree which regulate the volume flow of blood from the arteries into the capillaries. Ever since the pioneer experiments of Claude Bernard on the salivary glands, physiological evidence has supported the thesis that arteriolar dilatation increases capillary pressure and volume. Unused capillaries become patent; the filtration and flow of lymph are augmented (for recent work and references see Maurer (167)) and the organ or district affected increases in volume. This is the fundamental reaction in inflammatory hyperemia and is apparently the response of the frog's peripheral vessels to remote trauma (Zweifach, 268). As a result of such arteriolar dilatation, an increasing number of capillaries fill, and the venous flow from an organ at first increases; but, if widespread territories are involved, the arterial pressure declines and venous flow is reduced. Meanwhile, a volume of blood equal to that which remains in the capillaries is prevented from returning to the heart. It is not difficult to calculate that such an abstracted volume may be quite sizable (40, 127). It can be argued that such withdrawal occurs essentially from the arterial rather than the venous side and that total venous return may not be affected. However, the question cannot be settled by such *a priori* considerations because the regulation of the circulation, in intact mammals, is highly complicated. The direction and magnitude of the change in total venous return to the right auricle depends on the extent to which arterial pressures fall, on compensatory vasomotor or cardiac reactions and on translocation of fluid from various

blood reservoirs. Thus maximal dilatation of arterioles by nitrites leaves the total return flow and auricular pressures unaltered (258), whereas dilatation induced by histamine is said to reduce it in dogs, apparently because the hepatic venous flow is impeded (101).

The concept that primary arteriolar dilatation is an initiating agent in shock has been generally abandoned, largely because it had become so definitely associated with the theory of primary failure of the vasomotor center. It is not necessary to rehearse again the evidence which definitely proves that this is not an initiating factor (40, 42, 176, 201, 202). However, it is not compulsory to assume, particularly in toxemic forms of shock, that arteriolar dilatation is exclusively dependent on failure of a central or even a peripheral nervous mechanism; it could be caused by action of the same humoral agents which many believe to act on capillaries. Indeed, it is not improbable that, if any such agents exist, they might affect arterioles, capillaries and venules alike. Whether or not arteriolar dilatation occurs depends to some extent on the manner in which shock is produced. If the abdominal viscera are inspected shortly after a large hemorrhage or infliction of trauma, they are generally pale. By contrast, the rapid progressive reddening of intestines, mesentery and omentum which occurs when they are exposed and manipulated cannot have escaped surgeons or experimenters (162, 246). Capillary engorgement through vasodilatation is obvious; whether this is significant in reducing central venous pressure can be debated, and remains to be demonstrated.

The argument that primary arteriolar dilatation is excluded because, in shock, the decrease in cardiac output precedes the fall in blood pressure (Blalock, 29) is not a valid one. It is conceivable, and indeed probable, that primary dilatation, even in fairly extensive regions, could be compensated, *pari passu*, by cardiac acceleration and arteriolar constriction in other regions. Blalock's own experiments indicate a greater reduction of blood flow through limbs than elsewhere (30, 32). A similar compensation occurs very quickly in normal human subjects after inhalation of amyl nitrite; pressures are restored in 1 to 2 minutes, while the skin vessels obviously remain dilated. Compensatory constrictions might mobilize blood from the spleen (2, 12, 108, 115, 235), liver (15, 104, 142, 149, 187, 197), lungs (63, 130) and skin (13, 100, 187, 189, 207, 208), and this may be not merely sufficient to compensate for any local reduction in venous flow from organs involved but may even supply a larger return volume for the accelerated heart to pump.

In 1918, I (257) published arterial pressure pulses which seemed to indicate that reduction in peripheral resistance is a very early reaction

in shock due to intestinal manipulation and trauma. The intent of these inferences has apparently been misunderstood. It was never my belief that such reduction of peripheral resistance remains an important factor during the progressive decline of blood pressures but that, in types of shock studied, it might constitute an initial reaction which favors capillary stasis and reduction in effective circulatory volume. I am ready to grant, on the basis of broader experience, that the initial changes in the contour of pressure pulses may have another explanation, and that the evidence is not as crucial as I then believed. However, the changes in the form of the aortic pressure pulses then presented have never been controverted nor explained more satisfactorily by others. A study of changes in blood flow in the mesenteric arteries and portal vein correlated with alterations in the form of central pressure pulses is highly desirable during the early and progressive stages of shock. I hold no brief for this or any other conception as to how peripheral circulatory failure is initiated, but insist that it is inadvisable to cast aside too hastily the hypothesis of a primary visceral dilatation.

Primary arteriolar constriction. The conception that shock is initiated and maintained by virtue of an intense vasoconstriction had its origin in the clinic. It is difficult to assign priority to the idea; but, as is well known, it constituted the favored view among English clinicians from Mapother (165) to Malcolm (160). However, the clinical evidence and logic upon which this was based can no longer be regarded as satisfactory. The theory seemed to receive considerable support from experiments of Bainbridge and Trevan (9), of Erlanger and Gasser (76), and of Freeman et al. (89, 90, 91, 92, 93, 94), who demonstrated that reduction in blood volume, hemoconcentration and circulatory failure can be produced by prolonged administration of adrenalin or by compression of the aorta. The idea was given a real impetus by the often quoted experiments of Gesell (96, 97) who showed that, after hemorrhage or tissue abuse, the blood flow through the salivary glands and muscles decrease significantly before any fall of arterial pressure could be detected.

Since generalized arteriolar constriction *per se* reduces the capillary pressure and capacity in any territory, shrinks the organ affected and, in intact animals, often increases venous pressure and return (51), secondary mechanisms must exist to produce just the opposite effects characteristic of shock. Two possible mechanisms can be invoked:

1. The decreased capillary flow following an initial arteriolar constriction may cause an anoxic, asphyxial or ischemic action, which relaxes patent capillaries and opens up those ordinarily closed. If so,

capillary pressure would rise and filtration through the walls increase. Blood is not merely sequestered, but greater plasma leakage develops. Such stagnation of blood has at various times been placed in muscles (42, 234), in the intestinal mucosa (76, 126), in the liver (139), and, in addition, in the lungs (176). The concept accepts the findings of Krogh and his school (150) that capillaries possess the power of independent contractility and tonus. It is supported by observations of Landis (152) that temporary compression of afferent arterioles causes dilatation of the capillaries and allows the free passage of dyes. But it ignores equally valid observations of Clark and Clark (47) that capillaries change their size only in a passive manner.

2. If, as Zweifach (267) has recently claimed, the main nutritional capillaries are not directly interposed between the arteries and veins but represent a series of shunts, an extension of arteriolar constriction to the main A-V capillary would divert blood into the *real capillaries* causing the expansion of those in use and the opening of others not previously in action. Similar capillary filling may occur mechanically when larger arterio-venous shunts shut down (46) or when a second set of arterioles—as in the liver or kidney—constrict. This may explain the prompt increase in the volume of intestines or paws which has been reported after small doses of adrenalin (100).

Summarizing, it is possible, from a dynamic viewpoint, to postulate capillary stagnation after arteriolar constriction either on the basis of a passive process or of an active relaxation of the capillaries themselves.

Before we examine the evidence for and against the vasoconstriction theory it may be well to state that the theory has been given at least two separate interpretations. The more conservative hypothesis considers the original vasoconstriction as a compensatory mechanism which sustains arterial pressure and diverts blood to more vital organs, such as the heart and brain. But, if it persists until arterial pressures begin to decline it helps to throttle the blood supply generally, causing capillary stasis and loss of plasma. Such a conception which assigns a secondary evil effect to the compensatory constriction must be differentiated from the hypothesis, originated by Erlanger and associates and recently revived by Freeman (89, 90, 91, 92, 93, 94), that vasoconstriction is the initiating factor. According to Freeman, any overactivity of the sympathetic system or the adrenal medulla, of reflex or psychic origin, leads primarily to impairment of blood supply, induces capillary stasis and loss of plasma, and thus a reduction in circulatory volume and shock. Much of the experimental evidence originally supporting this hypothesis

was of a circumstantial nature. Experiments reported in 1933 (89) indicated that prolonged intravenous infusions of adrenalin in doses of 0.006 mgm./kilo/min. resulted in a reduction of the blood volume of cats, but no evidence was included that shock eventuated. Hamlin and Gregersen (114), using doses of 0.035 mgm./kilo/min., on the contrary, found an increase in blood volume of normal and sympathectomized cats. v. Prohaska, Harms and Dragstedt (203) were unable to produce shock in dogs by continuous administration of adrenalin for two weeks in doses of 0.0009 to 0.003 mgm./kilo/min. Recently, Freeman and his associates (91) were able to cause not only a reduction in blood volume but a decline of arterial pressure to shock levels by injection of adrenalin into atropinized, unanesthetized dogs at a rate of 0.0034 to 0.0164 mgm./kilo/min. for $\frac{1}{2}$ to $1\frac{1}{2}$ hours. Apparently, the subject merits further study. It still needs to be demonstrated that capillary congestion and increased permeability precede the reduction in blood volume and pressure and that the circulatory failure was not due to deleterious action of such prolonged injections on the heart.

The evidence for vasoconstriction. In order to implicate vasoconstriction as *the factor* responsible for the capillary engorgement, it is necessary to have substantial evidence 1, that arteriolar constriction occurs in the regions in which such capillary damage is most outstanding (e.g., in the intestines); 2, that it is sufficiently prolonged and intense to cause such capillary damage. In my judgment, neither has been demonstrated. Intense pallor of the skin is one of the conspicuous and persistent features of shock in man and, unquestionably, is due to intense arteriolar constriction. Good evidence exists, both in animals (179, 86, 216) and in man (94), that the volumes of limbs and their blood flow decrease materially during shock; further that the oxygen content of cutaneous venous blood is decreased and that the A-V oxygen difference is greater (6, 30, 122). It is remarkable, however, that despite such intense constriction and retardation of flow, cutaneous and somatic tissues do not exhibit any postmortem evidence of capillary damage (176). The facts do not fit together.

We may briefly examine the more direct experimental evidence which is so frequently quoted in support of the vasoconstrictor hypothesis. In 1909, Seelig and Lyon (225) found that the flow from a femoral vein measured for 5 second intervals decreased during shock, but no evidence was presented that this was not due to the steadily declining arterial pressures. The augmentation of flow which followed section of a sciatic nerve merely proved that vessels were still influenced by vasomotor

nerves but, of course, gave no evidence that the intensity of constriction exceeded the normal. In 1914, Mann (161) reported that normally innervated vessels in the tongues of dogs, ears of rabbits, and paws of kittens were constricted during shock in comparison with denervated vessels of an opposite side. Meek and Eyster (171) observed constriction of ear vessels during hemorrhage which led to *collapse of capillaries and venules*. Neither of these observations gives any support to the conception that vasoconstriction leads to capillary engorgment. Gesell in 1918 (96) demonstrated clearly that blood flow decreased markedly in the salivary gland, early in hemorrhage and after remote injuries to tissues; but the rest of his paper is pure speculation. Subsequently, Gesell and Moyle (97) demonstrated that the venous flow from a leg vein decreased during hemorrhage. Stagnation, edema or other deleterious influences in the glands or muscles were certainly not demonstrated.

In 1911 Cope (50), under my guidance, measured the rate of pressure decline in a temporarily occluded femoral artery, the collaterals of which had been ligated. He found an increased resistance in the leg vessels during early stages of hemorrhage and a decrease during the terminal stage. The method was again employed in 1922 by Forward and Perme (83) who found highly variable changes in resistance during shock, but, in general, they seemed to be in the direction of a decrease. Both of these investigators were careful in pointing out that changes in resistance so determined are not solely due to vasomotor changes but, in part, to changing venous pressure, blood viscosity, etc.

In 1912 Bartlett (16), under Erlanger's guidance, measured the rate at which a small volume of saline (ca. 2–5 cc.) under high pressure flowed into a leg artery "temporarily isolated from the circulation"—except for presence of numerous collaterals. Since such a small quantity of saline could obviously not reach all the arterioles and capillaries of the leg, the flow of the animal's own blood through these vessels was presumably determined. Hence changes in viscosity and variable collateral flow were perhaps not ruled out as completely as assumed. By this method, Bartlett found an increased rate of flow through the leg during early stages of shock. Erlanger, Gesell and Gasser (77) refined the method somewhat, and found, on the contrary, that the flow decreased through vessels of the limb and internal organs until late stages of shock. Similar results were apparently obtained by McKeen Cattell (44).

Perfusion of a hind-limb, a kidney or an inferior mesenteric vessel by larger volumes of saline solutions were carried out by several investigators. Such perfusions have the advantage that a solution of constant viscosity is being used, but the disadvantage that edema develops and

the flow decreases progressively through increasing extravascular pressures. Furthermore, the rôle of collateral circulations, which can increase rapidly after ischemia (71), is not evaluated. Using such methods, Morrison and Hooker (178) and Penfield (193) reported results which indicated that the flow increases as shock develops. In 1914, Pilcher and Sollmann (199) perfused the spleen, separated from the general circulation, but left in connection with the central nervous system, with saline solution. They reported an initial increase in resistance and a decrease during terminal stages of hemorrhage. It is questionable, however, whether the dog's spleen is a good test organ for studying vasomotor reactions, for it is very difficult to discount effects due to contraction of its muscular trabeculae. In any event, constriction of splenic vessels is certainly not followed by stasis of blood in capillaries and sinusoids, as demanded by the vasoconstriction hypothesis. Moreover, constriction of splenic vessels increases venous return and circulating volume. Recently the Mayo investigators (10), using the thermostromuhr, reported rapid and marked reduction in femoral arterial flow while blood pressure still remained elevated during early stages of shock.

Summarizing, 1, a number of investigations strongly indicate that arterioles of certain regions, particularly the limbs, salivary glands and spleen, constrict during shock, but this conclusion is by no means unanimous; 2, those who report occurrence of vasoconstriction have never described coincident or sequential capillary damage in regions studied, and 3, the organs selected for studying such vasomotor change may not be representative of changes in the splanchnic region, in which the most outstanding capillary damage seems to occur. If primary vasoconstriction can cause reduction in blood volume and shock, other facts are difficult to understand:

1. Intense and prolonged stimulation of pressor nerves, such as the sciatic or central vagus end, do not lead to shock or pathological changes in capillaries (42, 112, 161, 225, 258).

2. The somatic structures which undergo the most constriction fail to show signs of capillary congestion, edema and hemorrhage at autopsy.

3. The fact that stimulation of pressor nerves or injection of adrenalin (88), neosynephrin or related substances still cause substantial elevations of pressure during the course of shock strongly suggests that the arterioles are far from maximally constricted, as is sometimes claimed.

4. Prolonged anoxia of a degree far exceeding that which is probable after adrenalin causes serious symptoms in animals and man, but not those of shock (265).

To summarize, a critical examination of all experimental results sug-

gests that vasoconstriction may exist in certain territories of the body during shock, but there is no substantial evidence that it is sufficiently generalized or intense enough to cause the capillary damage which the hypothesis requires.

It remains to interpret the fact that cutaneous vessels are obviously constricted during shock. In the first place, it should be kept in mind that such cutaneous constriction occurs as a concomitant of many reactions in man which do not eventuate in shock, e.g., in gastric, biliary and renal colic, during acute gastric upsets, as a result of prolonged standing, preceding syncope due to nocuous influences and emotional reactions. In the second place, abundant experimental evidence exists that clamping of all limb vessels affects arterial pressure and calculated total resistance, scarcely, if at all (18, 262). On the other hand, the subpapillary plexus of the skin represents a large blood depot from which considerable volumes may be pressed into internal circuits by vasoconstriction. Thus, injection of small doses of adrenalin or cooling decreases the blood content of the skin significantly when an animal is warm (100, 207). Consequently, the purpose of the intense cutaneous constriction during and even preceding shock is not to help maintain arterial pressure by increasing total resistance, but to inaugurate a compensatory and perhaps an anticipatory reaction by virtue of which larger blood volumes are shifted internally for circulation through viscera (and muscles?).

Primary injury and dilatation of capillaries. Space is lacking to review the vast amount of experimental work which has demonstrated that many foreign substances or those extracted from body tissues cause, upon intravenous injection, circulatory changes which resemble those of shock in many respects. They include, Heidenhain's "lymphagogues of the first class," decomposition products and extracts of the intestinal mucosa, liver, traumatized muscle, etc., traumatized red cells (196), some bacterial toxins and products of inflammation (54, 173, 209), snake venoms, histamine, acetylcholine, adenylic compounds, etc. (For references see 127, 150, 152, 176.) Most of these are unquestionably capillary poisons which alter the size, turgor and permeability of capillary walls, causing stasis, increase in lymph flow, and later, tissue edema. Moreover, various substances (liver, minced muscle, bile, etc.), placed in the peritoneal cavity, cause similar generalized effects (176). These and other experimental evidences suggested that as yet unidentified substances, formed during high intestinal obstruction, gastro-intestinal perforations, toxemia and infections, may act directly upon capillaries and so initiate shock.

The hypothesis of primary capillary injury has recently been brought into prominence through the pathological studies of Moon and his associates. We have already indicated that the existence of visceral congestion, edema, effusions and petechial hemorrhages at autopsy have not been universally confirmed by pathologists. It seems probable that they are limited to certain types of shock. Moreover, even in forms of shock in which they exist, specimens obtained at autopsy cannot furnish *proof* that capillary dilatation and leakage were primary rather than terminal changes. I know of no positive and direct evidence that incipient capillary dilatation and loss of plasma from capillaries accounts for the *initial decrease* in venous return. Even so powerful a capillary dilator as histamine apparently increases capillary permeability only temporarily (183) and leads to irreversible circulatory failure only when some other factor is superimposed (166, 206). The bold interpretation that the apparent prophylactic and curative properties of cortico-adrenal substances (cf. p. 107) are due to maintenance or restoration of capillary permeability is mere speculation. In view of the wide acceptance which this idea has gained, it is surprising that so few attempts have been made to test it experimentally, with particular attention to the time of the capillary changes and their disappearance after treatment. The nearest approach to such studies are the recent reports of Menkin (173) and of Freed and Lindner (87) who found that adrenal cortical extracts and corticosterone prevent capillary leakage of trypan blue induced by leukotaxin, but these investigations obtained contradictory results from use of desoxycorticosterone. The applicability of such results to changes in permeability of shock induced by other agents than leucotaxin remains to be established; but the investigations at least represent a start in the right direction. The question whether leukotaxin may not be identical with histamine is not fully settled (212), and we still lack conclusive evidence as to whether the permeability valence of capillaries is determined chiefly by stretching (151) or by changes in the intracellular cement (45).

The wet and congested appearance of viscera in animals and individuals who die from shock has been considered helpful in accounting for the reduction in circulatory volume, particularly in types of shock in which plasma loss is not otherwise obvious. According to Moon (176), "further search for the location of the 'lost blood' is unnecessary." However, quantitative relations between the amount of plasma lost and that remaining in the vascular system cannot be established by postmortem examinations. The weights of organs and comparison with average normals also do not suffice, but even such comparisons have only

occasionally been attempted. Hence, while the circulatory volume is unquestionably reduced in forms of shock in which an obvious large loss to the exterior or into tissues can be demonstrated, the question of a similar reduction in toxemic forms of shock deserves more critical study.

Plasma depletion through capillary leakage is also frequently inferred from changes in viscosity and specific gravity of blood, from increased red cell counts, hemoglobin or hematocrit readings. As Adolph et al. (2), among others, has pointed out, it is hazardous to use red cell counts or hematocrit readings in estimating hemoconcentration or hemodilution in shock and hemorrhage, since red cells may be mobilized from the spleen and other blood banks. Even the dye methods which have not been employed too extensively in the study of toxemic shock are not as conclusive as was originally hoped. (For limitations see 75, 98, 105, 188.) Two difficulties—failure of complete mixing in regions of reduced blood flow and rapid leakage of dyes through capillaries—render deductions hazardous during shocklike states.

Summarizing, the magnitude of fluid loss from the vascular system through leaking capillaries has not been satisfactorily established in toxemic forms of shock. Consequently, the possibliity should be reexamined whether a change in the *effective* rather than the *actual* circulating volume may not be responsible for the reduced venous return in such conditions.

The problem of a toxic agent. If primary capillary dilatation is the result of a humoral factor, some form of toxic agent must exist. Of the many suspected agents, histamine has received the most thorough study. The earlier investigations of Dale, Laidlaw and Richards (56. 57, 58, 59) indicated that histamine injection, like shock, results in capillary stasis, transudation, increased gastro-intestinal secretions and lymph flow, and, later, edema, decrease in blood volume and reduction in arterial pressure. The conception that circulatory failure of traumatic shock is similarly due to absorption of histamine or a similar substance received what then seemed strong support. (For recent work see 7, 14, 65, 155, 157, 158.)

This was followed by a period during which experimental work began to question the guilt of histamine or, in fact, of any other toxic agent. Investigators are still not agreed as to whether the histamine content of blood is increased during shock (14, 48, 68, 69, 219), or whether blood from traumatized tissues contains more histamine (181, 182). Opinions are at variance as to whether any depressant substance is demonstrable (132, 190, 231, 232). If such toxic agents exist, transfusion of blood

from shocked dogs into normal animals may be expected to cause a fall of blood pressure in the recipient. Regarding the facts, experimenters are in apparently hopeless disagreement (3, 17, 22, 24, 49, 145, 148, 192, 218, 222, 253). However, the same situation exists regarding the humoral agents in hypertension; and it is questionable whether the problem can be settled by such injection studies.

Certain differences between circulatory reactions following injection of histamine and during shock have also been emphasized. According to Blalock (28), decrease in cardiac output precedes the decline of arterial pressure in shock, whereas the reverse is the case after histamine injections. The decrease in cardiac output is also much less in histamine shock (140). The bleeding volume required to cause death and the amount of blood that can be drained from organs after death is said to be much greater after histamine and other vasodilating agents than it is after shock induced by trauma (217). Partition of the return flow from various organs by ingenious methods led Blalock and Levy (32) to the conclusion that the venous flow is decreased proportionately from all parts of the body after histamine, but predominantly from the posterior extremity in shock following intestinal trauma and hemorrhage.

These differences are not necessarily of fundamental significance. The differing rates and portals of entry of injected and hypothetically absorbed histamine might account for these findings. When arterial and venous pressures and cardiometer tracings are recorded continuously during the course of a slow injection of histamine by femoral vein, reduction in venous pressure and stroke volume occur *pari passu* with, not after, the decline of blood pressure (personal observations with Werle).

To summarize, while histamine has not been finally excluded as the toxic agent, it is the consensus of opinion that it is not the agent concerned. If a toxic factor exists it is far more probable that a variety of agents rather than a common one is concerned. It may, as in the case of renin, require an activating agent and possible participation of an endocrine factor, which would explain the development of similar states of shock during cortico-adrenalin insufficiency.

Failure of a venopressor mechanism. The pressure component still available after blood has been driven through the capillaries into veins is the fundamental force which returns blood to the heart. Even with normal arterial pressures, its magnitude (ca. 16–17 mm. Hg), aided by a negative pressure of −3 to −4 mm. Hg in the thorax does not suffice to raise blood from the feet to the chest in the vertical position. It is

true that the hydrostatic pressure in the veins is counterbalanced by an equivalent hydrostatic pressure in the arteries, but, in order to become effective in returning blood to the heart in the vertical position capillary pressures in the feet would have to rise to values which would disorganize the exchange of fluid in the capillaries (Bazett, 20). It is obvious that some additional venopressor mechanism which helps the return of blood must exist. Its existence is also proved by the Riml experiment (211). This consists in suddenly clamping the pulmonary artery or stopping the heart, in which case pressures in the right auricle may rise to 9 to 10 mm. Hg, despite the fact that arteriolar pressure approaches zero.

The nature of this venopressor mechanism is still obscure, although authors of textbooks glibly repeat mechanisms not too surely demonstrated. The mechanisms suggested include *a*, extravascular support or compression of veins by an elastic tension of tissues and by the tonus or contraction of muscles; *b*, the pumping action of respiration (35), and *c*, active venomotor changes due to humoral or nervous actions (cf. Wiggers, 264; Bazett, 20).

We owe the suggestion that such a venopressor mechanism fails primarily in shock to Y. Henderson (122). It is no discredit that his conception as to the locus of the venopressor force appears to have changed in his search for this elusive mechanism. Originally, he postulated that lack of CO_2 relaxes small veins and smooth muscle around them, fills them with blood and thus reduces the effective circulating volume. Actual observations, that small veins increase in size during shock, are reported by a number of investigators (134, 164, 246, 268). With the evidence (5, 84, 133) that CO_2 relaxes muscles of the vascular system and gastro-intestinal tract, it proved equally easy to suggest that acapnial constriction hinders transmission of pressure from arterioles to veins and thus traps blood in the capillaries (124). Similar effects might be mediated by loss of tonus of the venomotor nerves, the presence of which seems to have been demonstrated for mesenteric (134, 135) as well as for superficial veins (11, 67, 70, 244). More recently, Henderson and his associates (125) reëmphasized the conception that "the tissue pressure throughout the body combined with negative intrathoracic pressure . . . determines venous return." Starling (234) had previously made a similar suggestion. The conception holds that the longitudinal pull of tonically contracted muscle fibers causes a transverse pressure against blood vessels lying between them and thus prevents loss of intracapillary pressure and fluid.

The experimental evidence, recently summarized by Henderson (121),

consists in observations that pressure measured by a hypodermic needle connected to a manometer and thrust into the biceps normally equals 60 to 90 mm. H_2O, that this pressure decreases during anesthesia and operations, and that it approaches zero at death. Apropos are observations of Gesell and Moyle (97) who report a "palpable softening" of muscles in unanesthetized dogs and a recorded lengthening in resting muscles of some anesthetized dogs following hemorrhage. Other studies (21, 119, 168) indicate that persons with relatively low tissue pressures are more prone to faint on standing (gravitational shock). The problems of whether such simple procedures as have been used to measure tissue pressure are really reliable and whether such tension is chiefly due to tension of fascia (249) require further study. In studying the relation of intramyocardial pressures to coronary flow, Gregg and Eckstein (107) were compelled to conclude that reliable measurements of supporting pressure had not yet been achieved. Similar critical studies are necessary with respect to skeletal muscle pressures before much stock can be taken in the conclusions regarding changes in tissue pressures during shock.

More general types of evidence make it highly improbable 1, that muscular tonus represents more than a subsidiary mechanism for the return of blood, and 2, that failure of such return is due to absence of motor impulses necessary for maintenance of skeletal muscle tonus. Loss of such tonus as a result of deep anesthesia, administration of curare in animals or during paresis or myasthenia gravis in man does not eventuate in shock. Furthermore, according to Moon, the muscles are particularly free from the congestion, hemorrhages and edema so conspicuous in the viscera during shock. Perhaps cessation of intestinal movements or loss of tone in smooth muscle of viscera might be concerned, though this has not been proved. Finally, the Riml experiment succeeds in flaccid anesthetized animals whose chests have been opened, and we have recently obtained evidence that this venopressor force—whatever its cause—still operates to raise venous pressures during the terminal stage of shock. The force for returning blood is reduced, but by no means lost.

Summarizing, while subsidiary forces unquestionably aid return of venous blood, there is no good evidence for the attractive hypothesis that failure of a venopressor mechanism constitutes an important factor in the initiation or progression of peripheral circulatory failure.

Summary regarding initiating factors. Our analysis indicates that while it is easy to set up views as to how the reduction of venous return is initiated, the operation of none of the suggested mechanisms—arteriolar dilatation or constriction, capillary dilatation and changes in perme-

ability, failure of a venopressor force—has been proved by existing experimental evidence. On the other hand, obvious loss of blood (hemorrhage) or plasma (e.g., in traumatic shock) remains a clearly demonstrated initiating factor in many types of shock. Whether a similar loss occurs through capillary leakage in other forms of peripheral circulatory failure and by what mechanisms it is induced are problems that require further relentless research.

This conclusion may have a bearing on the recurring question, as to best procedures for producing experimental shock for purposes of scientific study. The writer's reaction would be that, lacking crucial evidence that the primary decrease in venous return is due to any factor other than loss of blood or plasma, it would be a step *toward* the standardization of procedures, if investigators more generally chose a method which is known to cause such a primary decrease in circulatory volume. Adoption of such a plan would probably increase the consistency of results with respect to the efficacy of therapeutic procedures, the evoluting mechanisms, and the ultimate cause of irreversible circulatory failure.

Sustaining and Precipitating Mechanisms the Cause of Death. Following a suggestion by Gesell (96), writers continue to differentiate between initiating and sustaining factors in the causation of shock. The latter admirably discussed by Cannon (42), Blalock (29) and Harkins (117) include such developments as slowing of blood flow, lowering of metabolic rate, anoxia, acapnia (or hypercapnia), impaired renal excretion, alterations in acid-base balance, electrolytes of blood, etc. Concurrent dehydration through deprivation of water, profuse sweating, vomiting, diarrhea, lowering of body temperature, nervous reactions to fear and pain, prolonged anesthesia, concurrent effects of toxic products, infections, etc., may all contribute to a downward course. Lack of space prevents another review of their importance.

I have recently suggested (265, 266) that after a circulatory imbalance has been inaugurated by initiating factors, it still requires a precipitating mechanism (or agent) to convert it into a stage of irreversible circulatory failure. The precipitant may consist of a default in natural compensatory mechanisms or in the supervention of a new noxious factor.

That something breaks or defaults during the course of progressive circulatory failure and thus inaugurates an irreversible state is suggested by many facts gleaned partly from personal observations and partly from perusal of the literature on shock: 1. A laboratory procedure designed to produce experimental shock may result in only a moderate imbalance of the circulation which lasts for hours, when, quite suddenly,

a downward trend of blood pressure begins which leads speedily to a state of irreversible circulatory failure. 2. While shock which follows a progressive hemorrhage certainly starts with a decrease in circulating volume, inadequacy of venous return alone does not satisfactorily explain the terminal circulatory failure in all animals. Sometimes the central venous pressure even shows a premortal recovery. 3. Infusions of blood, plasma or even saline exert a highly beneficial effect during the early stages of shock, but they become ineffective or may even prove deleterious after an ill-defined non-reactive stage has been reached. 4. Identical procedures, standardized as far as individual laboratories are concerned, produce shock in some animals, but utterly fail to do so in others. More thought and experimental effort ought to be directed toward the cause of such resistance or refractoriness of animals and humans to shock. It is after all not strange that shock can be produced by catastrophies short of being fatal; it is, on the contrary, remarkable that the body may survive very drastic insults. In considering some of the factors which may be concerned in precipitating an irreversible circulatory state, we must again curb our desire to establish one dominant factor for all types of shock. A single prepotent factor may exist; but it is a better wager that a number are concerned.

The Time Factor; Ischemia; Irretrievable Capillary Damage. As long as blood pressure is maintained fairly well, the degree of vasoconstriction which exists throughout the course of shock is apparently not intense enough to reduce blood flow to damaging levels. Even with reduction in blood corpuscles, after considerable hemorrhage, no measurable anoxia may exist (99). On the other hand, abundant evidence supports the view that this may occur when the head of pressure in the aorta has become low. *A priori,* it seems probable that if such impairment of flow persists for a long time, it may have the same effect as a more temporary complete anemia. Penfield (193) adduced experimental evidence that the duration of low pressure is of importance in production of shock. However, it is surprising how well tissues or organs withstand a very low rate of blood flow before they cease to function or are unable to revive. If it were not for this factor, physiological perfusion experiments would never have reached the importance they have. Erlanger and Gasser (76) caused capillary damage and shock through ischemia produced by clamping of the aorta; but Quigley and Lindquist (204) and Parsons and Phemister (192) were not able to do so in unanesthetized animals. It should not be concluded too hastily that the differences were due to vital effects of anesthesia. The possibility that the intensity

of the ischemia was less owing to better collateral supply must be considered.

In our studies of hemorrhagic shock, Werle, Cosby, Wegria and I have, during the past year, studied many dogs that were kept at mean arterial pressures of 70 and 50 mm. Hg for 3 to 5 hours and others at 40 mm. Hg or less for shorter intervals. At the end of such periods of hypotension they were reinfused with all the blood (heparinized) lost by hemorrhage. Our experience coincides with that of others (e.g., 42, 162, 193) that many dogs recover from a hypotension of 50 mm. Hg maintained for 2 to $3\frac{1}{2}$ hours, whereas few are more than temporarily benefited by reinfusion when pressures have been at 30 to 35 mm. Hg for 45 to 60 minutes. Two factors are apparently of dominant importance,—the extent to which aortic pressure has been reduced and its duration. Examination of the mucosa of the upper intestine invariably showed intensive congestion, edema and hemorrhages with free blood or blood-tinged fluid in the lumen of those dogs that failed to recover. In those that did recover the abdominal viscera were pale or pink externally and the mucosa of the intestine either appeared normal or only slightly cyanotic and swollen. Such observations may have a bearing on the different pathological descriptions of the viscera after shock summarized on page 86. More important, however, they stress the fact that extensive capillary damage occurs only after a marked hypotension has existed for a considerable time. It is obviously a consequence, not a cause of the hypotension. Furthermore, it is by no means demonstrated that the failure of reinfusion to restore and maintain normal arterial pressures in non-surviving dogs is solely or even largely due to accumulation of all the reinjected blood in the intestinal mucosa or its lumen. Such an inference requires additional experimental support.

On the basis of many physiological studies of capillary behavior (for reviews see 150, 152), the development of complete capillary damage would be most expected under conditions in which anoxic or toxic actions come into play. Marked anoxia unquestionably exists during prolonged periods of decreased blood flow, but it is merely an inference that capillary endothelium is irretrievably damaged thereby. The increased lymph formed during extreme anoxia (118, 167) must have been completely returned to the circulation *via* lymphatic ducts in those experiments in which organs are reported "dry" at autopsy. Furthermore, histamine, which certainly exerts a very toxic action on capillaries, producing engorgement, edema and even petechial hemorrhages, does

not necessarily lead to irreversible shock even when administered over long periods of time. Without any desire to minimize capillary damage, it is hazardous to infer that such damage is solely responsible for the failure of response to blood or plasma transfusions.

Cortico-adrenal influences. Within recent years, the rôle of the adrenal cortex and its hormones in determining the resistance to shock-producing agents has received considerable attention. Studies on the effects of adrenalectomy and injection of progressively more purified hormones by a host of investigators were originally undertaken to clarify the cause of death from Addison's disease. During the course of such studies, it became increasingly more apparent to many observers that, while the functions of many organs are affected by adrenalectomy, the animals die in a state of circulatory failure which resembles shock from other causes. Swingle and his co-workers (237, 238, 239, 240, 241) presented evidence 1, that the reduction in effective blood volume and changes in blood chemistry after adrenalectomy are similar to those of shock and hemorrhage; 2, that animals in a profound state of shock can be revived by injection of cortical extracts and some purified products; 3, that adrenalectomized animals withstand less trauma and hemorrhage (cf. also 85); 4, that adrenalectomized animals regain their normal resistance if previously protected with large doses of cortical extracts, and 5, that shock cannot be produced by standard methods in normal animals who receive prophylactic doses of cortical hormone. They, therefore, suggested that the adrenal cortical hormones maintain normal capillary tone and permeability. As previously pointed out (p. 99), the evidence that the effects are due to an influence on capillaries is circumstantial. In somewhat similar experiments, Heuer and Andrus (129) also obtained beneficial effects, but only when cortico-adrenal extracts were given early. Perla et al. (194) believed that the resistance of rats to histamine is increased but this apparently occurs also after destruction of the adrenal medulla (137). Karody et al. (141) noted restoration of the histaminase content of the lungs after administration of cortico-adrenal extracts. Selye and his associates (229, 230) developed the concept that the adrenals, interrelated with the thymus and lymphatic tissues, furnish a defense mechanism whereby many tissues resist the deleterious effects of exposure, burns, spinal shock, acute infections, intoxications, etc. It may be theorized that, in some unknown way, additional amounts of appropriate adrenal substances are liberated by the cortex and that tissues gain an additional resistance as a result. If, however, the insult is prolonged or too severe the amount that can be provided

under stress is not adequate; hence cellular dysfunction, presumably including that of capillaries, begins. The funadmental idea seems to be a renovation of a familiar theory advanced some years earlier by Crile. It obviously requires many more facts for its establishment; but it does direct attention to a possible rôle of endocrine factors in resistance to shock. The promptness with which cardiac output and arterial pressures recover after administration of cortical substances to shocked animals is difficult to harmonize with the view that the only effect is to restore capillary tone and permeability, particularly since such restoration has not been demonstrated. The pharmacological actions of these substances on the heart and circulation also require a careful study in connection with such recoveries.

Translocation of potassium. The bulk of experimental work indicates that blood potassium increases under a variety of conditions involving excessive loss of sodium and water from the body, among them hemorrhage, shock due to trauma, intestinal obstruction or fistulas and injection of glucose intraperitoneally, etc. (For reviews see Scudder, 226; Fenn, 81; Harkins, 117.) Since all of these conditions eventuate in circulatory failure, Zwemer and Scudder (269), following a hint by Osterhout, put forward the hypothesis that the release of potassium by cell injury represents the long sought toxic agent in shock. Except in very extensive traumatization of tissues or wholesale destruction of red cells, such increase in potassium could scarcely be an initiating factor. Even in these conditions, its elimination in the urine and bile and its absorption by the liver would probably prevent the rise of blood potassium to toxic levels, much as happens upon ingestion of large doses of potassium salts. Furthermore, Thaler (243) has shown that the progressive increase in blood potassium which follows successive hemorrhages can be reduced again by re-injection of blood or saline, indicating the great mobility of potassium without tissue destruction. Fenn interprets such migration as evidence that intracellular, as well as extracellular, fluids are concerned in attempts to maintain a normal blood volume during hemorrhage.

It is conceivable, however, when the cell machinery begins to break down as a result of prolonged hypotension, that potassium is no longer able to diffuse back into cells and cannot be excreted. Then, the degree of hyperkalemia—or reduction in intracellular potassium—might be a deciding factor as to whether recovery of the circulation is possible or not. This would be in accordance with some observations that the most pronounced rise of serum potassium generally occurs during late

stages of shock (Scudder) and that reduction in blood flow itself increases the concentration of potassium (80), though not as much as was indicated by previous observations of Baetjer (8). While some investigations indicate that blood potassium increases during shock (for references see Scudder), others fail to find a consistent increase or a relationship to the severity of shock (25, 239, 240). Furthermore, elevation of potassium has been reported in other diseases, notably asthma and renal disorders, without evidence of shock symptoms (review, Myers and Muntwyler, 180).

The idea that hyperkalemia is a precipitating factor is not consonant with the fact that the cardiovascular changes which follow injection of potassium and those which occur in shock are strikingly different. Upon injection into normal animals, potassium causes vasoconstriction (62), whereas it is generally admitted that the vessels dilate in terminal stages of shock. There is no evidence that capillary congestion, edema and other signs of shock follow hyperkalemia. Large doses of potassium, administered by vein, affect cardiac rhythm and conduction before contractility and may lead to fibrillation (254, 261). Infusions of isotonic solutions over an hour are less harmful, but slow significant changes in the T wave and ST segment develop when plasma concentrations reach 5–10 m.Eq. per liter, and cessation of the heart beat occurs when they reach about 14–16 m.Eq. per liter (254). Similar changes have *not* been reported during the course of shock due to *any* agent. The possibility, of course, exists that conditions are not comparable. Studies of a possible accelerating effect of potassium injected during the course of shock experiments have not been made. After injection of potassium, its intracellular concentration tends to increase, whereas during shock it decreases. Furthermore, serum calcium is reported to rise during shock, and this has some ameliorating effect on the toxicity of potassium (254).

We must conclude that while hyperkalemia has not been proved to be a factor which precipitates circulatory failure, this important complication of shock deserves further study.

Reduction of blood volume to a critical minimum. According to a popular view, serious circulatory failure is precipitated when the effective circulating volume has been reduced to a level at which it can no longer be compensated by vasoconstriction, mobilization of blood from reservoirs and resorption of tissue fluid. With inadequate cardiac output, arterial pressures fall to low levels. Lowered arterial pressure combined with increasing viscosity reduces the pressure transmitted through capillaries into veins, thereby decreasing the primary venopressor force

still further. Obviously, a vicious cycle is started—venous return and cardiac output decrease more, etc.

If such a vicious cycle determined the irreversible state, venous pressure should continue to fall until the end. My observations (257) indicate that, after reaching a lower level, it remains stationary or may even rise somewhat toward the end. Furthermore, large infusions of blood or plasma are of temporary benefit only; the injected blood lodges in the spleen and intestinal vessels and cannot be returned to the heart (personal observations with Werle). Apparently, at a certain stage an adequate circulation cannot be restored by merely filling the system as one does an automobile radiator.

We may conclude that progressive reduction of blood volume *per se* is not the precipitating factor but probably is indirectly responsible for it.

Default of compensatory or emergency mechanisms. Rein (206) has recently summarized investigations from his laboratory which suggest that failure or fatigue of certain emergency mechanisms may constitute the precipitating factor. These mechanisms include: 1. Local chemical agents and axon reflexes which cause constriction or relaxation of minute vessels in accordance with local needs. 2. Extrinsic reflexes from surrounding tissues or from special organs (e.g., in the kidney and mesentery) which exercise a determinate influence on the regions in which they arise. 3. Intrinsic vascular reflexes, mediated essentially by the sinus and aortic nerves, which help to maintain an adjusted action of the cardiac pump, and an adequate aortic pressure so that localized mechanisms can operate. 4. Collateral reflexes which apparently exempt regions that require a better blood flow from participation in the emergency reactions.

We can probably assume that such variable and often conflicting adjustments of peripheral pressures and flow are not a matter of chance but are integrated, to some extent at least, by the central nervous system. Furthermore, the possibility exists that either as a result of bombardment by afferent impulses, e.g., from the site of trauma, or owing to decrease in blood flow to the brain and cord (95, 198), the efficiency of such integration is reduced or abolished altogether during the development of a progressive circulatory imbalance. The conception accords with the fragmentary observations that carotid sinus reflexes are less effective when blood pressures are low (147, 236), that they fatigue easily with repetitive clamping of the carotids (72), and that animals whose blood pressure has been reduced by hemorrhage or trauma withstand less additional hemorrhage or trauma than those whose blood pres-

sure is lowered by vasodilatation (217). Such diminished resistance also follows sympathectomy (93) and previous removal of the spleen (153). However, section of the carotid sinus and aortic nerves still produces a further fall in blood pressure after hemorrhage (185, 236).

If as some experiments indicate (31, 33, 159, 190, 230*a*, 231, 232), but other investigations do not support (22, 53), afferent impulses play a rôle in production of shock they may do so through disorganization of central integrated control of the circulation. Obviously, this is a problem of neurophysiology as well as one of cardiovascular dynamics, and requires specialized apparatus and training for its study. We cannot hope to solve these problems with equipment restricted to a mercury manometer, an induction coil, and a hammer for pounding muscles.

Vasomotor failure. Extensive reflex arteriolar dilatation may occur as an incipient reaction *during* many catastrophies which lead to shock. These should not be confused with vasomotor failure for it appears to have been amply demonstrated that the vasomotor center remains active and perhaps hyperactive during the development of shock. However, many investigators (50, 77, 178, 199) who reported decreased regional flow during the progress of hemorrhage or shock, found an increased flow[5] during late stages. Consequently, more careful study of the temporal relation of such changes to the blood pressure may reveal that rapid vasomotor failure constitutes a precipitating mechanism. The sudden circulatory collapse which occasionally occurs under a variety of experimental conditions and unhappily terminates an important experiment is difficult to explain otherwise than by such vasomotor failure. We have seen it occur during dynamic experiments in which venous and initial intraventricular pressure as well as cardiac output remained unimpaired while blood pressure steadily fell. Infusions of saline solution or blood or stimulation of pressor nerves are relatively ineffective in restoring arterial pressures, whereas epinephrine, neosynephrin and related substances increase arterial pressures more than can be attributed to increased cardiac output. Other experimenters have undoubtedly had similar experiences. Ivy (personal communication), for example, informs me that he has observed similar reactions after stimulation of the central vagus under certain conditions, and following insult to the lungs and pleura.

Werle, Cosby and I, recently found that, when extreme hypotension has existed for several hours as a result of regulated bleeding, simultaneous stimulation of both vagus nerves still causes tremendous pressor effects in some dogs, but none in others. Since epinephrine and neosyne-

[5] At equivalent perfusion pressures.

phrine still cause large elevations of pressure in the latter, we suspect that vasomotor center failure was the precipitating mechanism in these animals. At any event, the time has arrived when it should no longer be considered a sin to give thought to the possible rôle that the vasomotor center may play in determining the lethal character of peripheral circulatory failure.

Myocardial depression. The conception that the myocardium is not affected during shock has become almost an axiom among experimenters. This is doubtless an overstatement and is chiefly based on demonstrations that saline or blood infusions produce, at least temporarily, an increased cardiac output and significant elevations of arterial pressures toward normal. However, the proposition that cardiac filling and expulsion are just as effective in the shocked as in the normal animal at equivalent filling pressures has never been put to an experimental test. In other words, the applicability during shock of laws formulated by Henderson and Starling has not received a thorough study. We have been impressed with the possibility that the myocardium is depressed by three common observations in advanced stages of shock, viz.: 1. In some dogs, venous pressure tends to rise again, suggesting passive congestion. 2. The heart tends to slow after hemorrhage or shock has progressed. 3. Infusion of blood or plasma may raise venous pressures far above normal levels without producing the anticipated increase in cardiac output or blood pressure. 4. When artificial respiration is maintained, progressive myocardial failure definitely terminates any shock experiment.

Myocardial depression may moreover be predicted *a priori* since prolonged hypotension obviously decreases coronary flow significantly. This is compensated to some extent by the diminished work which the left ventricle has to perform, but the work of the right ventricle does not decrease as significantly. Unless, therefore, unknown compensatory reactions occur which augment coronary flow beyond that anticipated from hemodynamic considerations, an anoxic depression of the myocardium seems probable. Therefore, the possibility that depression of the myocardium through impairment of coronary flow or insidious action of possible toxic agents may represent the critical factor for recovery or complete failure of the circulation, deserves further study. That some primary depression of the myocardium exists in some instances seems certain; whether it is of decisive inportance in the causation of irreversible circulatory failure still remains a question.

The problem of aortic adaptation. In discussing the possible increase

in the capacity of the vascular system during shock only the dominant changes in the smaller vessels of the circuit are generally considered. That the capacity and elasticity of the aorta and its branches may likewise be altered during shock has until recently seemed highly improbable. Reports can be found in the literature which indicate that the size of the aorta and its immediate branches (223) may not be adjusted entirely passively by the internal pressures (for review see Bazett, 19). In view of the paucity of muscular elements demonstrable histologically, and their questionable arrangement for effective action, the writer has been among those who regarded such reports as based on concealed technical errors. Quite unexpectedly, however, Wegria and I (263) found during temporary hypertension produced by reflexes and epinephrine, that the aorta, after a temporary (passive) expansion, progressively decreased in size.

Preliminary experiments reported by Werle and Cosby (251) showed that some dogs, after maintenance of a low arterial pressure by repeated hemorrhage, failed to recover when the blood withdrawn was all reinfused. A study of the forms of the optical pressure pulses recorded after such reinfusion showed significant changes. As in previous experiments on shock reported by the writer (257), these changes might be due to a greatly reduced peripheral resistance. They could, however, equally well be attributed to a different mode and volume of ejection or to a relaxed state of the aorta. The remote possibility that failure of mechanisms which adapt the size and elasticity to changing volumes and pressures of blood may be a decisive factor in circulatory failure needs to be investigated.

Summary of precipitating factors. Our own impressions and those gleaned from a review of pertinent literature on shock are that while venous return is reduced relatively early in shock and represents the chief factor in its continuance, such a decrease alone does not suffice to create the irreversible circulatory failure characteristic of deep shock. Consequently, the suggestion is ventured that some as yet unidentified precipitatory mechanism or several of these in association exists. A number of possible factors—the adrenal cortex and its hormones, translocation of potassium, default of emergency reflex controls, vasomotor failure, myocardial depression and lack of aortic adaptation—are suggested for further study in this connection.

THE SEQUENCE OF DYNAMIC EVENTS DURING HEMORRHAGE AND SHOCK. During the past year (1940–41), Doctors Werle, Cosby and I performed miscellaneous experiments on hemorrhage, designed to cast further light

on moot dynamic problems arising from a coincident re-survey of recent literature for this review. As a result, my conceptions of the sequence of events in hemorrhage (255) and shock (257) have been revised somewhat, as follows: (1) The similarity of changes (quantitative and qualitative) in the central arterial pressure pulses during hemorrhage and shock indicate that the dynamic sequence is the same in both; except that, in traumatic shock, vasodilatation may be a temporary prelude. This is, in fact, comparable to primary shock; it is caused by direct actions or local reflexes in intestinal exposure and manipulation and, reflexly, in trauma accompanied by other intensive nervous reactions. The transient character of this reaction precludes its detection in connection with time-consuming gasometric measurements of cardiac output, and it is, therefore, consistently missed in such studies. It is still questionable whether these preliminary changes have any bearing on the subsequent secondary shock that develops.

(2) Owing to the operation of compensatory mechanisms, the circulating volume may be slowly decreased by a significant amount (ca. 35 per cent) before arterial pressure declines; in fact, it may elevate. This well-known fact has been conveniently explained by acceleration of the heart and increased total peripheral resistance, due to fairly generalized vasoconstriction. Evidence now available makes it more probable that blood pressure is sustained chiefly because cardiac output is not decreased at once. In order to accomplish this a normal venous return must be maintained. My present conception is that vasoconstriction is not universal and acts not so much by increasing total peripheral resistance—which is doubtful—as by driving blood from certain blood reservoirs—spleen, skin and liver—into the large veins. Whether the veins contract in addition, as some (39, 101, 127) have claimed, I am not prepared to say. Vasoconstriction is also helpful in reducing capillary pressures in selective areas, thereby favoring the resorption of tissue fluid, which according to Adolph (1) is practically complete within 22 minutes after a single large hemorrhage. This constitutes a second line of defense in maintaining a normal venous return. During this early stage of hemorrhage there is no determinable increase in the oxygen utilization coefficient nor impairment of blood flow (99), hence *initial* deterioration of capillary tone through vasoconstriction seems to be a figment of the imagination. Capillary damage is more probably a consequence than a cause of arterial hypotension.

(3) The second stage, generally inaugurated by a moderate decline of arterial blood pressure and striking changes in the contour of the pres-

sure pulses begins when compensatory mechanisms are no longer able to maintain venous return; consequently, cardiac output decreases. Whether additional vasoconstriction at this stage can compensate by effecting an increased total peripheral resistance requires further study; this probably varies in different animals. In accordance with all evidence, the progressive decline in blood pressure to lower levels is almost wholly due to a progressively decreasing cardiac output. During these stages, reinfusion of blood or plasma leads to complete recovery. Following this, either of two events supervenes: The circulatory failure may continue fairly steadily on its downward course or, after blood pressure has been stabilized for several hours at levels ranging from 78 to 50 mm. Hg, it drops rather abruptly, and death occurs with certainty within one-half to one hour.

In the latter type, precipitating mechanisms are almost certainly concerned. The abrupt intensification of the downward course must be differentiated from one due to cessation of respiration, an occasional accident in anesthetized animals. While it occurs during the period of decreasing respiratory rate and depth, we have so far been unable to link the sudden failure to a possible arterial anoxemia or to default of a respiratory pressor influence on venous return, but this deserves further study.

Two precipitating causes for the circulatory collapse which follows seem to operate, failure of the vasomotor center and failure of the heart; but the operation of other mechanisms cannot be excluded. After the irreversible failure has begun, transfusions of blood or plasma may restore cardiac output, but blood pressures and pressure pulses are never restored to normal and the improvement is transient. Within another hour or less, progressive failure rapidly leads to a similar mode of death. Inspection of viscera during the course of such temporary recovery and decline, or at autopsy, reveals that much of the transfused blood accumulates in the spleen and mucosa of the small intestines. As engorgement of the mucosal vessels increases, some rupture and cause a bloody intestinal fluid. The stomach and colon are not congested but generally remain pale. Such observations clearly indicate that something happens in the peripheral circulation during late stages of hemorrhage which leads to congestion and rupture of capillaries. The evidence available in the literature reviewed does not as yet permit expression of a final opinion as to how this is brought about.

In conclusion, if in these discussions the author has appeared unnecessarily disputatious in accepting generally favored notions, let it be understood that counter-emphasis in the interpretation of known facts

is sometimes made designedly in the hope that others may be stimulated to produce more crucial evidence or more cogent arguments for their beliefs.

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